Medical Cannabis Wikibook

Cannabis

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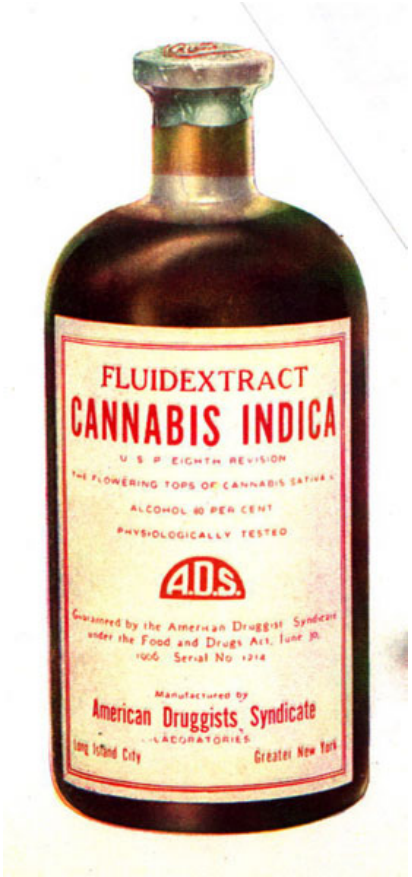
Medical cannabis

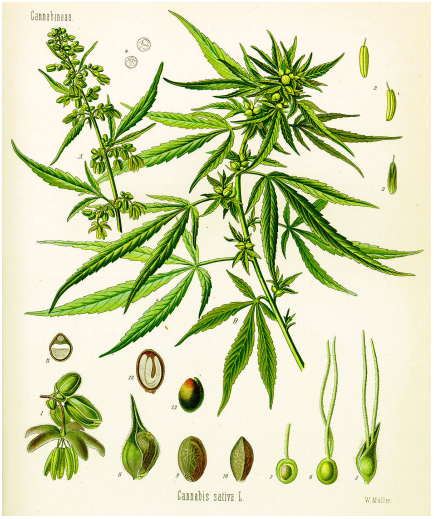
Medical cannabis refers to the parts of the herb cannabis used as a physician-recommended form of medicine or herbal therapy, or to synthetic forms of specific cannabinoids such as THC as a physician-recommended form of medicine. The *Cannabis* plant has a long history of use as medicine, with historical evidence dating back to 2737 BCE.[1] Cannabis is one of the 50 "fundamental" herbs of traditional Chinese medicine,[2] and is prescribed for a broad range of indications.

American *Cannabis indica* purchased at a medical cannabis dispensary.



Cannabis indica fluid extract, American Druggists Syndicate, pre-1937.

Use



Cannabis as illustrated in Köhler's book of medicinal plants from 1897

Medical cannabis is illegal in most countries. A number of governments, including the U.S. Federal Government, allow treatment with one or more specific low doses of synthetic cannabinoids for one or more disorders.

Supporters of medical cannabis argue that cannabis does have several well-documented beneficial effects.[3][4][5][6] Among these are: the amelioration of nausea and vomiting, stimulation of hunger in chemotherapy and AIDS patients, lowered intraocular eye pressure (shown to be effective for treating glaucoma), as well as gastrointestinal illness. Its effectiveness as an analgesic has been suggested—and disputed—as well.

There are several methods for administration of dosage, including vaporizing or smoking dried buds, drinking, or eating extracts, and taking capsules. The comparable efficiency of these methods was the subject of an investigative study[6] conducted by the National Institutes of Health.

Synthetic cannabinoids are available as prescription drugs in some countries. Examples are Marinol (The United States and Canada) and Cesamet (Canada, Mexico, the United Kingdom, and the United States).

While utilizing cannabis for recreational purposes is illegal in many parts of the world, many countries are beginning to entertain varying levels of decriminalization for medical usage (the medical marijuana movement), including Canada, Austria, Germany, Switzerland, the Netherlands, Czech Republic, Spain, Israel, Italy, Finland, and Portugal. In the United States, federal law outlaws all use of herb parts from Cannabis, while some states have approved use of herb parts from Cannabis as medical cannabis in conflict with federal law. The United States Supreme Court has ruled in *United States v. Oakland Cannabis Buyers' Coop* and *Gonzales v. Raich* that the federal government has a right to regulate and criminalize cannabis, even for medical purposes. A person can therefore be prosecuted for a cannabis-related crime even if it is medical cannabis that is legal according to the laws of this state.

Clinical applications

"Victoria", the United States' first legal medical marijuana plant grown by The Wo/Men's Alliance for Medical Marijuana.

A 2002 review of medical literature by Franjo Grotenhermen states that medical cannabis has established effects in the treatment of nausea, vomiting, premenstrual syndrome, unintentional weight loss, insomnia, and lack of appetite. Other "relatively well-confirmed" effects were in the treatment of "spasticity, painful conditions, especially neurogenic pain, movement disorders, asthma, [and] glaucoma".[7]

Preliminary findings indicate that cannabis-based drugs could prove useful in treating inflammatory bowel disease, migraines, fibromyalgia, and related conditions.[8]

Medical cannabis has also been found to relieve certain symptoms of multiple sclerosis[9] and spinal cord injuries[10][11][12] by exhibiting antispasmodic and muscle-relaxant properties as well as stimulating appetite.

Other studies state that cannabis or cannabinoids may be useful in treating alcohol abuse,[13] amyotrophic lateral sclerosis,[14][15] collagen-induced arthritis,[16] asthma,[17] atherosclerosis,[18] bipolar disorder,[19][20] colorectal

cancer,[21] HIV-Associated Sensory Neuropathy[22] depression,[23][24][25][26] dystonia,[27] epilepsy,[28][29][30] digestive diseases,[31] gliomas,[32][33] hepatitis C,[34] Huntington's disease,[35] leukemia,[36] skin tumors,[37] methicillin-resistant *Staphylococcus aureus* (MRSA),[38] Parkinson's disease,[39] pruritus,[40][41] posttraumatic stress disorder (PTSD),[42] psoriasis,[43] sickle-cell disease,[44] sleep apnea,[45] and anorexia nervosa.[46] Controlled research on treating Tourette syndrome with a synthetic version of tetrahydrocannabinol, (brand name Marinol) (the main psychoactive chemical found in cannabis), showed the patients taking Marinol had a beneficial response without serious adverse effects;[47][48] other studies have shown that cannabis "has no effects on tics and increases the individuals inner tension".[49] Case reports found that cannabis helped reduce tics, but validation of these results requires longer, controlled studies on larger samples.[50][51]

A study done by Craig Reinarman surveyed among why people in California used cannabis and it found many reasons why people had used cannabis. It was used to relieve pain, muscle spasms, headaches, anxiety, nausea, vomiting, depression, cramps, panic attacks, diarrhea, and itching. Others used cannabis to improve sleep, relaxation, appetite, concentration or focus, and energy. Some patients used it to prevent medication side effects, anger, involuntary movements, and seizures, while others used it as a substitute for other prescription medications and alcohol.[52]

Recent studies

Safety of cannabis

Cannabis smoke contains thousands of organic and inorganic chemical compounds. This tar is chemically similar to that found in cigarette smoke and includes many of the same carcinogens.[53]

Deaths attributed directly to cannabis usage are infrequent but have been documented. [54] [55] [56] Cannabis related deaths are more widespread. [57]

From January 1997 to June 2005, the U.S. Food and Drug Administration (FDA) reported zero deaths caused by the primary use of cannabis. In contrast, common FDA-approved drugs which are often prescribed in lieu of cannabis (such as anti-emetics and anti-psychotics), were the primary cause of 10,008 deaths.[58] The cannabinoid THC has an extremely low toxicity and the amount that can enter the body through the consumption of cannabis plants poses no threat of death.[59]

Various strains of medical marijuana in front of a vaporizer

Cannabis smoke contains substances that can damage DNA and increase the risk of cancer just like tobacco smoke, though no definitive link between cannabis and cancer has been found.[60] Cancer causing chemicals in cannabis smoke have been found in amounts 50% higher than those found in tobacco smoke. According to the British Lung Foundation, smoking three to four joints (cannabis cigarettes) a day has been found to be associated with the same degree of damage to tissue in the airways of the lung as 20 or more tobacco cigarettes a day.[61]

The Journal of the American Medical Association released findings from a 20-year study that bolstered evidence that cannabis doesn't do the kind of damage tobacco does. Analysis of over 5,000 smokers showed that cannabis did not appear to harm lung function, although cigarettes did. Cigarette smokers' scores worsened steadily over the course of the study. Participants who smoked up to 1 joint daily for 7 years, or 1 joint weekly for 20 years, were not linked with worse scores. Dr Donald Tashkin suggested the reason for this might be that cannabis helps fight inflammation and may counteract the effects of irritating chemicals in the drug.[60] The study concluded: "Occasional and low cumulative marijuana use was not associated with adverse effects on pulmonary function".[62]

Cannabis usage has been shown to negatively affect the ability to drive safely.[63] The British Medical Journal recently indicated that "Drivers who consume cannabis within three hours of driving are nearly twice as likely to cause a vehicle collision as those who are not under the influence of drugs or alcohol"[64]

Glaucoma

In glaucoma, cannabis and THC have been shown to reduce intra-ocular pressure (IOP) by an average of 24% in people with normal IOP who have visual-field changes. In studies of healthy adults and glaucoma patients, IOP was reduced by an average of 25% after smoking a cannabis "cigarette" that contained approximately 2% THC—a reduction as good as that observed with most other medications available today, according to a review by the Institute of Medicine.[65]

Medical cannabis in edible form

In a separate study, the use of cannabis and glaucoma was tested and found that the duration of smoked or ingested cannabis or other cannabinoids is very short, averaging 3 to 3.5 hours. Their results showed that for cannabis to be a viable therapy, the patient would have to take in cannabis in some form every 3 hours. They said that for ideal glaucoma treatment it would take two times a day at most for compliance purposes from patients.[66]

Spasticity in multiple sclerosis

A review of six randomized controlled trials of a combination of THC and CBD extracts for the treatment of multiple sclerosis (MS) related muscle spasticity reported, "Although there was variation in the outcome measures reported in these studies, a trend of reduced spasticity in treated patients was noted." The authors postulated that "cannabinoids may provide neuroprotective and anti-inflammatory benefits in MS."[67] A small study done on whether or not cannabis could be used to control tremors of MS patients was conducted. The study found that there was no noticeable difference of the tremors in the patients. Although there was no difference in the tremors the patients felt as if their symptoms had lessened and their quality of life had improved. The researchers concluded that the mood enhancing or cognitive effects that cannabis has on the brain could have given the patients the effect that their tremors were getting better.[68][69]

Medical cannabis

Alzheimer's disease

Research done by the Scripps Research Institute in California shows that the active ingredient in marijuana, THC, prevents the formation of deposits in the brain associated with Alzheimer's disease. THC was found to prevent an enzyme called acetylcholinesterase from accelerating the formation of "Alzheimer plaques" in the brain more effectively than commercially marketed drugs. THC is also more effective at blocking clumps of protein that can inhibit memory and cognition in Alzheimer's patients, as reported in Molecular Pharmaceutics.[70] Cannabinoids can also potentially prevent or slow the progression of Alzheimer's disease by reducing tau protein phosphorylation, oxidative stress, and neuroinflammation.[71]

Breast cancer

According to a 2007 study at the California Pacific Medical Center Research Institute, cannabidiol (CBD) may stop breast cancer from spreading throughout the body.[72] These researchers believe their discovery may provide a non-toxic alternative to chemotherapy while achieving the same results minus the painful and unpleasant side effects. The research team says that CBD works by blocking the activity of a gene called Id-1, which is believed to be responsible for a process called metastasis, which is the aggressive spread of cancer cells away from the original tumor site.[72]

HIV/AIDS

Investigators at Columbia University published clinical trial data in 2007 showing that HIV/AIDS patients who inhaled cannabis four times daily experienced substantial increases in food intake with little evidence of discomfort and no impairment of cognitive performance. They concluded that smoked cannabis has a clear medical benefit in HIV-positive patients.[73][74] In another study in 2008, researchers at the University of California, San Diego School of Medicine found that marijuana significantly reduces HIV-related neuropathic pain when added to a patient's already-prescribed pain management regimen and may be an "effective option for pain relief" in those whose pain is not controlled with current medications. Mood disturbance, physical disability, and quality of life all improved significantly during study treatment.[75] Despite management with opioids and other pain modifying therapies, neuropathic pain continues to reduce the quality of life and daily functioning in HIV-infected individuals. Cannabinoid receptors in the central and peripheral nervous systems have been shown to modulate pain perception. No serious adverse effects were reported, according to the study published by the American Academy of Neurology.[76] A study examining the effectiveness of different drugs for HIV associated neuropathic pain found that smoked Cannabis was one of only three drugs that showed evidence of efficacy.[77]

Brain cancer

A study by Complutense University of Madrid found the chemicals in cannabis promote the death of brain cancer cells by essentially helping them feed upon themselves in a process called autophagy. The research team discovered that cannabinoids such as THC had anticancer effects in mice with human brain cancer cells and in people with brain tumors. When mice with the human brain cancer cells received the THC, the tumor shrank. Using electron microscopes to analyze brain tissue taken both before and after a 26- to 30-day THC treatment regimen, the researchers found that THC eliminated cancer cells while leaving healthy cells intact.[78] The patients did not have any toxic effects from the treatment; previous studies of THC for the treatment of cancer have also found the therapy to be well tolerated. However, the mechanisms which promote THC's tumor cell–killing action are unknown.[78]

Opioid dependence

Injections of THC eliminate dependence on opiates in stressed rats, according to a research team at the *Laboratory for Physiopathology of Diseases of the Central Nervous System* (France) in the journal *Neuropsychopharmacology*.[79] Deprived of their mothers at birth, rats become hypersensitive to the rewarding effect of morphine and heroin (substances belonging to the opiate family), and rapidly become dependent. When these rats were administered THC, they no longer developed typical morphine-dependent behavior. In the striatum, a region of the brain involved in drug dependence, the production of endogenous enkephalins was restored under THC, whereas it diminished in rats stressed from birth which had not received THC. Researchers believe the findings could lead to therapeutic alternatives to existing substitution treatments.[79]

In humans, drug treatment subjects who use cannabis intermittently are found to be more likely to adhere to treatment for opioid dependence.[80] Historically, similar findings were reported by Edward Birch, who, in 1889, reported success in treating opiate and chloral addiction with cannabis.[81]

Controlling ALS symptoms

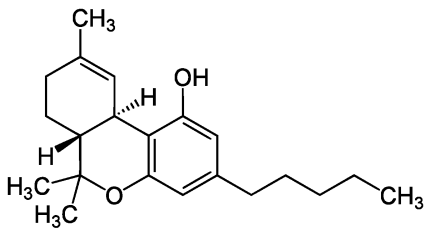
Recent research has been conducted on if the use of cannabis could control some of the symptoms of ALS or Lou Gehrig's Disease. A survey was conducted on 131 people who suffered from ALS. The survey asked if the subjects had used cannabis in the last 12 months to control some of their symptoms. The survey resulted in 13 people who had used the drug in some form to control symptoms. The survey results found that cannabis was moderately effective in reducing symptoms of appetite loss, depression, pain, spasticity, drooling and weakness and the longest relief reported was for depression. The pattern of symptom relief was consistent with those reported by people with other conditions, including multiple sclerosis (Amtmann et al. 2004).[68]

Medicinal compounds

Cannabis contains 483 compounds. At least 80 of these are cannabinoids,[82][83][84] which are the basis for medical and scientific use of cannabis. This presents the research problem of isolating the effect of specific compounds and taking account of the interaction of these compounds.[85] Cannabinoids can serve as appetite stimulants, antiemetics, antispasmodics, and have some analgesic effects.[86] Six important cannabinoids found in the cannabis plant are tetrahydrocannabinol, tetrahydrocannabinolic acid, cannabidiol, cannabinol, β-caryophyllene, and cannabigerol.

Tetrahydrocannabinol

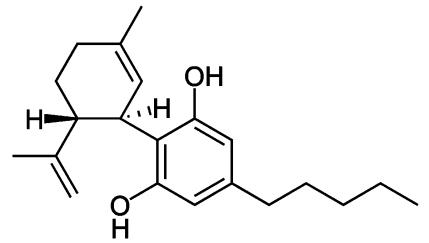
Tetrahydrocannabinol (THC) is the primary compound responsible for the psychoactive effects of cannabis. The compound is a mild analgesic, and cellular research has shown the compound has antioxidant activity.[87] THC is believed to interact with parts of the brain normally controlled by the endogenous cannabinoid neurotransmitter, anandamide.[88][89] Anandamide is believed to play a role in pain sensation, memory, and sleep.



Chemical structure of tetrahydrocannabinol (THC)

Cannabidiol

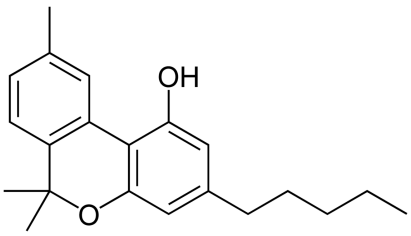
Cannabidiol (CBD) is a major constituent of medical cannabis. CBD represents up to 40% of extracts of medical cannabis.[91] Cannabidiol has been shown to relieve convulsion, inflammation, anxiety, cough, congestion and nausea, and it inhibits cancer cell growth.[90] Recent studies have shown cannabidiol to be as effective as atypical antipsychotics in treating schizophrenia.[92] Because cannabidiol relieves the aforementioned symptoms, cannabis strains with a high amount of CBD may benefit people with multiple sclerosis, frequent anxiety attacks and Tourette syndrome.[67][90][93]



Cannabidiol has been shown to relieve convulsions, inflammation, anxiety, cough, congestion and nausea, and it inhibits cancer cell growth.[90]

Cannabinol

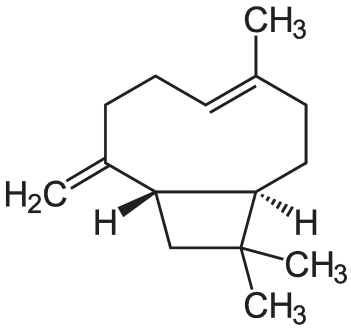
Cannabinol (CBN) is a therapeutic cannabinoid found in *Cannabis sativa* and *Cannabis indica*.[94] It is also produced as a metabolite, or a breakdown product, of tetrahydrocannabinol (THC).[95] CBN acts as a weak agonist of the CB_1 and CB_2 receptors, with lower affinity in comparison to THC.[96][97]



Structure of Cannabinol

β-Caryophyllene

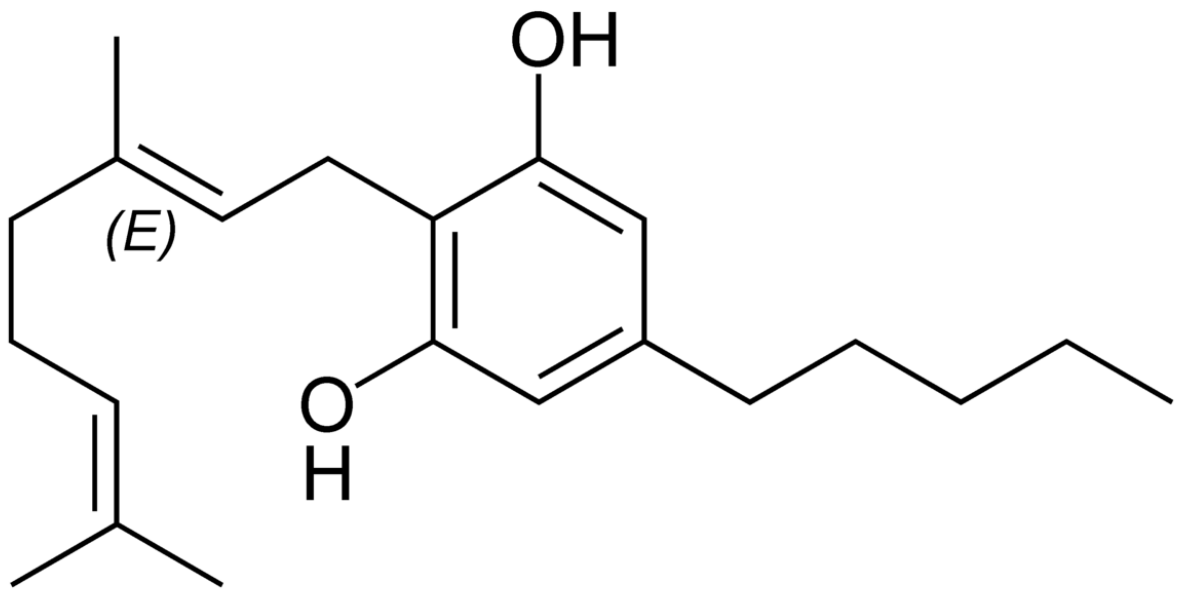
Part of the mechanism by which medical cannabis has been shown to reduce tissue inflammation is via the compound β-caryophyllene.[98] A cannabinoid receptor called CB2 plays a vital part in reducing inflammation in humans and other animals.[98] β-Caryophyllene has been shown to be a selective activator of the CB2 receptor.[98] β-Caryophyllene is especially concentrated in cannabis essential oil, which contains about 12–35% β-caryophyllene.[98]



Chemical structure of β-caryophyllene

Cannabigerol

Like cannabidiol, cannabigerol is not psychoactive. Cannabigerol has been shown to relieve intraoccular pressure, which may be of benefit in the treatment of glaucoma.[99][100]



Cannabigerol.

Pharmacologic THC and THC derivatives

In the USA, the FDA has approved several cannabinoids for use as medical therapies: dronabinol (Marinol) and nabilone. These medicines are taken orally.

These medications are usually used when first line treatments for nausea and vomiting associated with cancer chemotherapy fail to work. In extremely high doses and in rare cases "psychotomimetic" side effects are possible. The other commonly used antiemetic drugs are not associated with these side effects.

Canasol is a cannabis-based medication for glaucoma that relieves intraocular pressure symptoms associated with late-stage glaucoma.

It was created by an ophthalmologist, Dr. Albert Lockhart and Dr. Manley E. West, and began distribution in 1987.[101][102] As of 2003, it was still being distributed in the United Kingdom, several US states, and several Caribbean nations.[103]

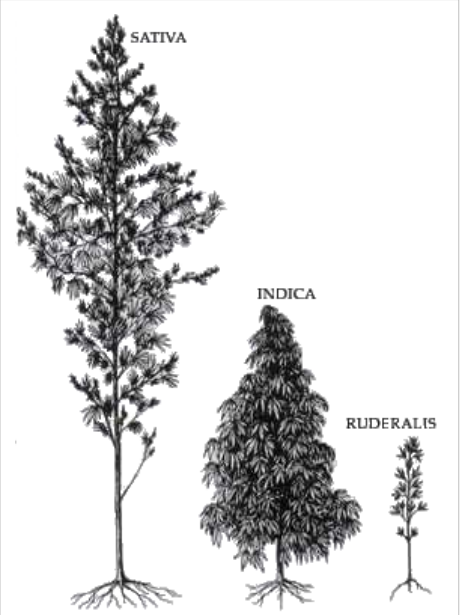
It is notable for being one of the first cannabis-containing pharmaceuticals to be developed for the modern pharmaceutical market and being one of the few such pharmaceuticals to have ever been legally marketed in the United States.[102][104]

The prescription drug Sativex, an extract of cannabis administered as a sublingual spray, has been approved in Canada for the adjunctive treatment (use along side other medicines) of both multiple sclerosis and cancer related pain.[105][106] Sativex has also been approved in the United Kingdom, New Zealand, and the Czech Republic, and is expected to gain approval in other European countries.[107][108][109] William Notcutt is one of the chief researchers that has developed Sativex, and he has been working with GW and founder Geoffrey Guy since the company's inception in 1998. Notcutt states that the use of MS as the disease to study "had everything to do with politics."[110]

Medication	Approval	Country	Licensed indications	Cost
Nabilone	1985	USA, Canada	Nausea of cancer chemotherapy that has failed to respond adequately to other antiemetics	US$ 4000.00 for a year's supply (in Canada)[111]
Canasol	1987	USA, Canada, several Caribbean nations	Introcular pressure associated with late-stage Glaucoma	
Marinol	1985	USA Canada (1992)	Nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional treatments	US$ 652 for 30 doses @ 10 mg online[112]
	1992	USA	Anorexia associated with AIDS–related weight loss[113]	
Sativex	1995	Canada	Adjunctive treatment for the symptomatic relief of neuropathic pain in multiple sclerosis in adults	C$ 9,351 per year[114]
	1997	Canada	Pain due to cancer	

Difference between *Cannabis indica* and *Cannabis sativa*

Cannabis indica may have a CBD:THC ratio 4–5 times that of *Cannabis sativa*. Cannabis strains with relatively high CBD:THC ratios are less likely to induce anxiety than vice versa. This may be due to CBD's antagonistic effects at the cannabinoid receptors, compared to THC's partial agonist effect. CBD is also a 5-HT_{1A} receptor agonist, which may also contribute to an anxiolytic effect.[115] This likely means the high concentrations of CBD found in *Cannabis indica* mitigate the anxiogenic effect of THC significantly.[115] The effects of *sativa* are well known for its cerebral high, hence used daytime as medical cannabis, while *indica* are well known for its sedative effects and preferred night time as medical cannabis.[115]



Cannabis sativa, *Cannabis indica*, and *Cannabis ruderalis*

Criticism

One of the major criticisms of cannabis as medicine is opposition to smoking as a method of consumption. However, smoking is no longer necessary due to the development of healthier methods. Today, medicinal cannabis patients can use vaporizers, where the essential cannabis compounds are extracted and inhaled. In addition, edible cannabis, which is produced in various baked goods, is also available, and has demonstrated longer lasting effects.

The United States Food and Drug Administration (FDA) issued an advisory[116] against *smoked* medical cannabis stating that, "marijuana has a high potential for abuse, has no currently accepted medical use in treatment in the United States, and has a lack of accepted safety for use under medical supervision. The National Institute on Drug Abuse NIDA state that "Marijuana itself is an unlikely medication candidate for several reasons: (1) it is an unpurified plant containing numerous chemicals with unknown health effects; (2) it is typically consumed by smoking further contributing to potential adverse effects; and (3) its cognitive impairing effects may limit its utility".[117]

The Institute of Medicine, run by the United States National Academy of Sciences, conducted a comprehensive study in 1999 to assess the potential health benefits of cannabis and its constituent cannabinoids. The study concluded that smoking cannabis is not recommended for the treatment of any disease condition, but did conclude that nausea, appetite loss, pain and anxiety can all be mitigated by marijuana. While the study expressed reservations about smoked cannabis due to the health risks associated with smoking, the study team concluded that until another mode of ingestion was perfected that could provide the same relief as smoked cannabis, there was no alternative. In addition, the study pointed out the inherent difficulty in marketing a non-patentable herb. Pharmaceutical companies will not substantially profit unless there is a patent. For those reasons, the Institute of Medicine concluded that there is little future in smoked cannabis as a medically approved medication. The report also concluded that for certain patients, such as the terminally ill or those with debilitating symptoms, the long-term risks are not of great concern.[118][119]

Marinol was less effective than the steroid megestrol in helping cancer patients regain lost appetites.[120] A phase III study found no difference in effects of an oral cannabis extract or THC on appetite and quality of life (QOL) in patients with cancer-related anorexia-cachexia syndrome (CACS) to placebo.[121] "Citing the dangers of cannabis and the lack of clinical research supporting its medicinal value" the American Society of Addiction Medicine in March 2011 issued a white paper recommending a halt to using marijuana as a medicine in U.S. states where it has been declared legal.[122][123]

Mental disorders

A study of 50,000 Swedish soldiers who had smoked at least once were twice as likely to develop schizophrenia as those who had not smoked. The study concluded that either smoking caused a higher rate of schizophrenia, or that those with schizophrenia were more likely to be drawn to cannabis.[124]

A study by Keele University commissioned by the British government found that between 1996 and 2005 there had been significant reductions in the incidence and prevalence of schizophrenia. From 2000 onwards there were also significant reductions in the prevalence of psychoses.

The authors say this data is "not consistent with the hypothesis that increasing cannabis use in earlier decades is associated with increasing schizophrenia or psychoses from the mid-1990s onwards".[125]

A 10 year study on 1923 individuals from the general population in Germany, aged 14–24, concluded that cannabis use is a risk factor for the development of incident psychotic symptoms. Continued cannabis use might increase the risk for psychotic disorder.[126]

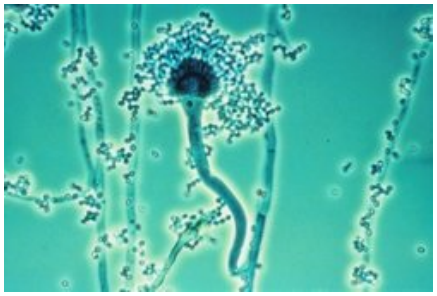
Lung cancer and chronic obstructive pulmonary disease

The evidence to date is conflicting as to whether smoking cannabis increases the risk of developing lung cancer or chronic obstructive pulmonary disease (COPD) among people who do not smoke tobacco. In 2006 a study by Hashibe, Morgenstern, Cui, Tashkin, *et al.* suggested that smoking cannabis does not, by itself, increase the risk of lung cancer. Many studies did report a strongly synergistic effect, however, between tobacco use and smoking cannabis such that tobacco smokers who also smoked cannabis dramatically increased their already very high risk of developing lung cancer or chronic obstructive pulmonary disease by as much as 300%. Some of these research results follow below:

- In 2006, Hashibe, Morgenstern, Cui, Tashkin, *et al.* presented the results from a study involving 2,240 subjects that showed non-tobacco users who smoked marijuana did not exhibit an increased incidence of lung cancer or head-and-neck malignancies. These results were supported even among very long-term, very heavy users of marijuana.[127] Tashkin, a pulmonologist who has studied cannabis for 30 years, commenting in news reports in the lay media on the results of the study he co-authored, suggested, "It's possible that tetrahydrocannabinol (THC) in cannabis smoke may encourage apoptosis, or programmed cell death, causing cells to die off before they have a chance to undergo malignant transformation". He summarized the results found by his study, saying "We hypothesized that there would be a positive association between cannabis use and lung cancer, and that the association would be more positive with heavier use. What we found instead was no association at all, and even a suggestion of some protective effect."[128][129]
- A case-control study of lung cancer in adults 55 years of age and younger found that the risk of lung cancer increased 8% (95% confidence interval (CI) 2–15) for each joint-year of cannabis smoking, after adjustment for confounding variables including cigarette smoking, and 7% (95% CI 5–9) for each pack-year of cigarette smoking, after adjustment for confounding variables including cannabis smoking.[130]
- A 2008 study by Hii, Tam, Thompson, and Naughton found that cannabis smoking leads to asymmetrical bullous disease, often in the setting of normal CXR and lung function. In subjects who smoke cannabis, these pathological changes occur at a younger age (approximately 20 years earlier) than in tobacco smokers.[131]
- Researchers from the University of British Columbia presented a study at the American Thoracic Society 2007 International Conference showing that smoking cannabis and tobacco together more than tripled the risk of developing COPD over just smoking tobacco alone.[132] Similar findings were released in April 2009 by the Vancouver Burden of Obstructive Lung Disease Research Group. The study reported that smoking both tobacco and cannabis synergistically increased the risk of respiratory symptoms and COPD. Smoking only cannabis, however, was not associated with an increased risk of respiratory symptoms of COPD.[133] In a related commentary, pulmonary researcher Donald Tashkin wrote, "...we can be close to concluding that cannabis

smoking by itself does not lead to COPD".[134]

Harm reduction



Aspergillus fumigatus

The harm caused by smoking can be minimized or eliminated by the use of a vaporizer[135] or ingesting the drug in an edible form. Vaporizers are devices that heat the active constituents to a temperature below the ignition point of the cannabis, so that their vapors can be inhaled. Combustion of plant material is avoided, thus preventing the formation of carcinogens such as polyaromatic hydrocarbons, benzene and carbon monoxide. A pilot study led by Donald Abrams of UC San Francisco showed that vaporizers eliminate the release of irritants and toxic compounds, while delivering equivalent amounts of THC into the bloodstream.[136] According to Matthew Seamon and his co-authors “Vaporizers are the optimal route of administration because they allow for rapid and complete absorption with minimal combustible byproducts, often considered the major health risk associated with smoking tobacco.”[137]

In order to kill microorganisms, especially the molds *A. fumigatus*, *A. flavus* and *A. niger*, Levitz and Diamond suggested baking marijuana at 150 °C (302 °F) for five minutes. They also found that tetrahydrocannabinol (THC) was not degraded by this process.[138]

Organizational positions

A number of medical organizations have endorsed reclassification of marijuana to allow for further study. These include, but are not limited to:

- The American Medical Association[69][139][140]
- The American College of Physicians – America's second largest physicians group[141]
- Leukemia & Lymphoma Society – America's second largest cancer charity[142]
- American Academy of Family Physicians opposes the use of marijuana except under medical supervision[143]

Other medical organizations recommend a halt to using marijuana as a medicine in U.S.

- The American Society of Addiction Medicine[122][123]

History

Ancient China and Taiwan

The use of cannabis, at least as fiber, has been shown to go back at least 10,000 years in Taiwan. "Dà má" (Pinyin pronunciation) is the Chinese expression for cannabis, the first character meaning "big" and the second character meaning "hemp."

Cannabis, called *má* 麻 (meaning "hemp; cannabis; numbness") or *dàmá* 大麻 (with "big; great") in Chinese, was used in Taiwan for fiber starting about 10,000 years ago.[144] The botanist Li Hui-Lin wrote that in China, "The use of Cannabis in medicine was probably a very early development. Since ancient humans used hemp seed as food, it was quite natural for them to also discover the medicinal properties of the plant."[145] The oldest Chinese pharmacopeia, the (ca. 100 CE) *Shennong Bencaojing* 神農本草經 ("Shennong's Materia Medica Classic"), describes *dama* "cannabis".

> The flowers when they burst (when the pollen is scattered) are called 麻蕡 [*mafen*] or 麻勃 [*mabo*]. The best time for gathering is the 7th day of the 7th month. The seeds are gathered in the 9th month. The seeds which have entered the soil are injurious to man. It grows in [Taishan] (in [Shandong] ...). The flowers, the fruit (seed) and the leaves are officinal. The leaves and the fruit are said to be poisonous, but not the flowers and the kernels of the seeds.[146]

In the early 3rd century CE, Hua Tuo was the first person known to use cannabis as an anesthetic. He reduced the plant to powder and mixed it with wine for administration.[147] In China, the era of Han Western, the iii th century the great surgeon Hua Tuo conducts operations under anesthesia using Indian hemp. The Chinese term for anesthesia (麻醉: má zui) is also composed of the ideogram which means hemp, followed by means of intoxication. Elizabeth Wayland Barber says the Chinese evidence "proves a knowledge of the narcotic properties of *Cannabis* at least from the 1st millennium B.C." when *ma* was already used in a secondary meaning of "numbness; senseless." "Such a strong drug, however, suggests that the Chinese pharmacists had now obtained from far to the southwest not THC-bearing *Cannabis sativa* but *Cannabis indica*, so strong it knocks you out cold.[148]

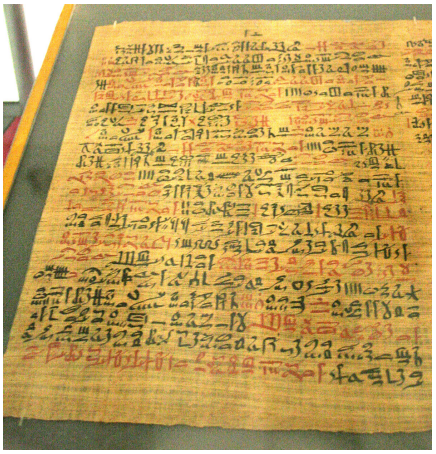
Cannabis is one of the 50 "fundamental" herbs in traditional Chinese medicine,[2] and is prescribed to treat diverse indications.

> Every part of the hemp plant is used in medicine; the dried flowers (勃), the achenia (蕡), the seeds (麻仁), the oil (麻油), the leaves, the stalk, the root, and the juice. The flowers are recommended in the 120 different forms of (風 *feng*) disease, in menstrual disorders, and in wounds. The achenia, which are considered to be poisonous, stimulate the nervous system, and if used in excess, will produce hallucinations and staggering gait. They are prescribed in nervous disorders, especially those marked by local anaesthesia. The seeds, by which is meant the white kernels of the achenia, are used for a great variety of affections, and are considered to be tonic, demulcent, alterative, laxative, emmenagogue, diuretic, anthelmintic, and corrective. They are made into a congee by boiling with water, mixed with wine by a particular process, made into pills, and beaten into a paste. A very common mode of exhibition, however, is by simply eating the kernels. It is said that their continued use renders the flesh firm and prevents old age. They are prescribed internally in fluxes, post-partum difficulties, aconite poisoning, vermillion poisoning, constipation, and obstinate vomiting. Externally they are used for eruptions, ulcers, favus, wounds, and falling of the hair. The oil is used for falling hair, sulfur poisoning, and dryness of the throat. The leaves are considered to be poisonous, and the freshly expressed juice is used as an anthelmintic, in scorpion stings, to stop the hair from falling out and to prevent it from turning grey. They are especially thought to have antiperiodic properties. The stalk, or its bark, is considered to be diuretic, and is used with other drugs in gravel. The juice of the root is used for similar purposes, and is also thought to have a beneficial action in retained placenta and post-partum hemorrhage. An infusion of hemp (for the preparation of which no directions are given) is used as a demulcent drink for quenching thirst and relieving fluxes.[149]

“Medical use of cannabis included, rheumatism, intestinal constipation, female reproductive system disorders, malaria, and other uses” (Zuardi, 2006, 4).

Ancient Egypt

The Ebers Papyrus (ca. 1550 BCE) from Ancient Egypt describes medical cannabis.[150] Other ancient Egyptian papyri that mention medical cannabis are the Ramesseum III Papyrus (1700 BC), the Berlin Papyrus (1300 BC) and the Chester Beatty Medical Papyrus VI (1300 BC).[151] The ancient Egyptians even used hemp (cannabis) in suppositories for relieving the pain of hemorrhoids.[152] Around 2,000 B.C., the ancient Egyptians used cannabis to treat sore eyes.[153] The egyptologist Lise Manniche notes the reference to "plant medical cannabis" in several Egyptian texts, one of which dates back to the eighteenth century BCE.[154]



The Ebers Papyrus (ca. 1550 BCE) from Ancient Egypt has a prescription for medical marijuana applied directly for inflammation

Ramesseum III Papyrus (1700 BC)

Papyrus Ramassei III, col. 26:
K.t phr.t: mɜt.t šmšm.t qnqn, sḏr n ỉɜd.t, ỉ^{c} ỉr.ty n=s ỉm dwɜy
Alia praecepta:parsley, hemp and obey, in the dew of rest, wash eyes in that early in the morning

Ancient India

Surviving texts from ancient India confirm that cannabis' psychoactive properties were recognized, and doctors used it for treating a variety of illnesses and ailments. These included insomnia, headaches, a whole host of gastrointestinal disorders, and pain: cannabis was frequently used to relieve the pain of childbirth.[155]

In India, the use of cannabis was widely disseminated, both as a medicine and as a recreational drug. Such a broad use may be due to the fact that cannabis maintained a straight association with religion, which assigned sacred virtues to the plant” (Zuardi, 2006, 3).

Ancient Greece

The Ancient Greeks used cannabis to dress wounds and sores on their horses.[156]

In humans, dried leaves of cannabis were used to treat nose bleeds, and cannabis seeds were used to expel tapeworms.[156] The most frequently described use of cannabis in humans was to steep green seeds of cannabis in either water or wine, later taking the seeds out and using the warm extract to treat inflammation and pain resulting from obstruction of the ear.[156]

In the 5th century BCE Herodotus, a Greek historian, described how the Scythians of the Middle East used cannabis in steam baths.[156]

The Ancient Greeks used cannabis not only for human medicine, but also in veterinary medicine to dress wounds and sores on their horses.[156]

South East Asia

Patani from Asia are primary natural producers of the diuretic, antiemetic, antiepileptic, anti-inflammatory, pain killing and antipyretic properties of *Cannabis sativa*, and used it extensively for 'Kopi Kapuganja' and 'Pecel Ganja', as recreation food, drinks and relaxing medication for centuries.

Medieval Islamic world

In the medieval Islamic world, Arabic physicians made use of the diuretic, antiemetic, antiepileptic, anti-inflammatory, pain killing and antipyretic properties of *Cannabis sativa*, and used it extensively as medication from the 8th to 18th centuries.[157]

Cannabis sativa from *Vienna Dioscurides*, 512 AD

Modern history

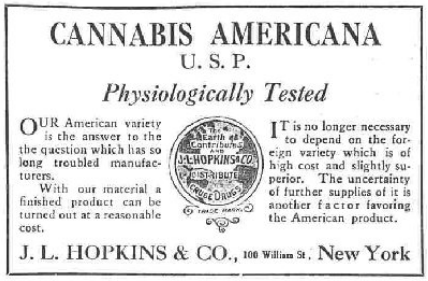
An Irish physician, William Brooke O'Shaughnessy, is credited with introducing the therapeutic use of cannabis to Western medicine. He was Assistant-Surgeon and Professor of Chemistry at the Medical College of Calcutta, and conducted a cannabis experiment in the 1830s, first testing his preparations on animals, then administering them to patients in order to help treat muscle spasms, stomach cramps or general pain.[158]

Medical cannabis ad from Sweden (1800)

Cannabis as a medicine became common throughout much of the Western world by the 19th century. It was used as the primary pain reliever until the invention of aspirin.[159] Modern medical and scientific inquiry began with doctors like O'Shaughnessy and Moreau de Tours, who used it to treat melancholia and migraines, and as a sleeping aid, analgesic and anticonvulsant. At the local level authorities introduced various laws that required the mixtures that contained cannabis, that was not sold on prescription, must be marked with warning labels under the so-called poison laws.[160]

A Swedish lexicon printed in 1912 describes cannabis drug and cannabis extract as a now with us deserted method for medical treatment.[161]

There were at least 2000 cannabis medicines prior to 1937 with over 280 manufacturers.[162]


CANNABIS AMERICANA
U. S. P.
Physiologically Tested
OUR American variety is the answer to the the question which has so long troubled manufacturers.
With our material a finished product can be turned out at a reasonable cost.
IT is no longer necessary to depend on the foreign variety which is of high cost and slightly superior. The uncertainty of further supplies of it is another factor favoring the American product.
J. L. HOPKINS & CO., 100 William St., New York

An advertisement for cannabis americana distributed by a pharmacist in New York in 1917.

Later in the century, researchers investigating methods of detecting cannabis intoxication discovered that smoking the drug reduced intraocular pressure.[163] In 1955 the antibacterial effects were described at the Palacký University of Olomouc. Since 1971 Lumír Ondřej Hanuš was growing cannabis for his scientific research on two large fields in authority of the University. The marijuana extracts were then used at the University hospital as a cure for aphthae and haze.[164] In 1973 physician Tod H. Mikuriya reignited the debate concerning cannabis as medicine when he published "Marijuana Medical Papers". High intraocular pressure causes blindness in glaucoma patients, so he hypothesized that using the drug could prevent blindness in patients. Many Vietnam War veterans also found that the drug prevented muscle spasms caused by spinal injuries suffered in battle.[165] Later medical use focused primarily on its role in preventing the wasting syndromes and chronic loss of appetite associated with chemotherapy and AIDS, along with a variety of rare muscular and skeletal disorders.

In 1964, Dr. Albert Lockhart and Manley West began studying the health effects of traditional cannabis use in Jamaican communities. They discovered that Rastafarians had unusually low glaucoma rates and local fishermen were washing their eyes with cannibis extract in the belief that it would improve their sight. Lockhart and West developed, and in 1987 gained permission to market, the pharmaceutical Canasol: one of the first to cannabis extracts. They continued to work with cannabis throughout the years, developing more pharmaceuticals and eventually receiving the Jamaican Order of Merit for their work.[102]

Later, in the 1970s, a synthetic version of THC was produced and approved for use in the United States as the drug Marinol. It was delivered as a capsule, to be swallowed. Patients complained that the violent nausea associated with chemotherapy made swallowing capsules difficult. Further, along with ingested cannabis, capsules are harder to dose-titrate accurately than smoked cannabis because their onset of action is so much slower. Smoking has remained the route of choice for many patients because its onset of action provides almost immediate relief from symptoms and because that fast onset greatly simplifies titration. For these reasons, and because of the difficulties arising from the way cannabinoids are metabolized after being ingested, oral dosing is probably the least satisfactory route for cannabis administration.[166] Relatedly, some studies have indicated that at least some of the beneficial effects that cannabis can provide may derive from synergy among the multiplicity of cannabinoids and other chemicals present in the dried plant material.[167] Such synergy is, by definition, impossible with respect to the use of single-cannabinoid drugs like Marinol.

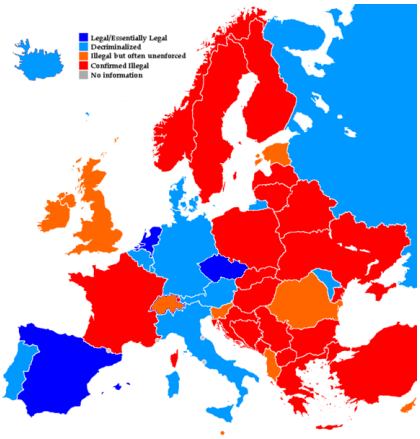
During the 1970s and 1980s, six U.S. states' health departments performed studies on the use of medical cannabis. These are widely considered some of the most useful and pioneering studies on the subject. Voters in eight states showed their support for cannabis prescriptions or recommendations given by physicians between 1996 and 1999, including Alaska, Arizona, California, Colorado, Maine, Michigan, Nevada, Oregon, and Washington, going against policies of the federal government.[168]

In May 2001, "The Chronic Cannabis Use in the Compassionate Investigational New Drug Program: An Examination of Benefits and Adverse Effects of Legal Clinical Cannabis" (Russo, Mathre, Byrne et al.) was completed. This three-day examination of major body functions of four of the five living US federal cannabis patients found "mild pulmonary changes" in two patients.[169]

Cannabis female flowers closeup with trichomes (white). These plant parts contain the highest concentration of medicinal compounds.

National and international regulations

Medical use of cannabis or preparation containing THC as the active substance is legalized in Canada, Belgium, Austria, Netherlands, UK, Spain, Israel, Finland and some states in the U.S., although it is still illegal under U.S. federal law.



European laws on cannabis possession (small amount). Data are from multiple sources detailed on the full source list

Cannabis is in Schedule IV of the United Nations´ Single Convention on Narcotic Drugs, making it subject to special restrictions. Article 2 provides for the following, in reference to Schedule IV drugs:[170]

> *A Party shall, if in its opinion the prevailing conditions in its country render it the most appropriate means of protecting the public health and welfare, prohibit the production, manufacture, export and import of, trade in, possession or use of any such drug except for amounts which may be necessary for medical and scientific research only, including clinical trials therewith to be conducted under or subject to the direct supervision and control of the Party.*

The convention thus allows countries to outlaw cannabis for all non-research purposes but lets nations choose to allow medical and scientific purposes if they believe total prohibition is not the most appropriate means of protecting health and welfare. The convention requires that states that permit the production or use of medical cannabis must operate a licensing system for all cultivators,manufacturers and distributors and ensure that the total cannabis market of the state shall not exceed that required "for medical and scientific purposes."[170]

Africa

Cannabis has been used in Africa since the 15th century. Its use was introduced by Arab traders, somehow connected to India. “In Africa, the plant was used for snake bite, to facilitate childbirth, malaria, fever, blood poisoning, anthrax, asthma, and dysentery.” (Zuardi, 2006, 4) Though African government has tried to limit and stop its use, it still seems to be deeply ingrained, mostly through religious rituals.

Austria

In Austria both Δ^9-THC and pharmaceutical preparations containing Δ^9-THC are listed in annex V of the Narcotics Decree (*Suchtgiftverordnung*).[171] Compendial formulations are manufactured upon prescription according to the German *Neues Rezeptur-Formularium*.[172][173]

On July 9, 2008, the Austrian Parliament approved cannabis cultivation for scientific and medical uses.[174] Cannabis cultivation is controlled by the Austrian Agency for Health and Food Safety (*Österreichische Agentur für Gesundheit und Ernährungssicherheit, AGES*).[175]

Canada

In Canada, the regulation on access to cannabis for medical purposes, established by Health Canada in July 2001, defines two categories of patients eligible for access to medical cannabis. BC College of Physicians and Surgeons’ recommendation, as well as the CMPA position, is that physicians may prescribe cannabis if they feel comfortable with it. The MMAR forms are a confidential document between Health Canada, the physician and the patient. The information is not shared with the College or with the RCMP. No doctor has ever gone to court or faced prosecution for filling out a form or for prescribing medical cannabis.[176] Category 1 covers any symptoms treated within the context of providing compassionate end-of-life care or the symptoms associated with medical conditions listed below:

Centre compassion de Montréal, au Québec.

- severe pain and/or persistent muscle spasms from multiple sclerosis, from a spinal cord injury, from spinal cord disease,
- severe pain, cachexia, anorexia, weight loss, and/or severe nausea from cancer or HIV/AIDS infection,
- severe pain from severe forms of arthritis, or
- seizures from epilepsy.

Category 2 is for applicants who have debilitating symptom(s) of medical condition(s), other than those described in Category 1. The application of eligible patients must be supported by a medical practitioner.[177]

The cannabis distributed by Health Canada is provided under the brand CannaMed by the company Prairie Plant Systems Inc. In 2006, 420 kg of CannaMed cannabis was sold, representing an increase of 80% over the previous year.[178] However, patients complain of the single strain selection as well as low potency, providing a pre-ground product put through a wood chipper (which deteriorates rapidly) as well as gamma irradation and foul taste and smell.[179]

It is also legal for patients approved by Health Canada to grow their own cannabis for personal consumption, and it's possible to obtain a production license as a person designated by a patient. Designated producers were permitted to grow a cannabis supply for only a single patient, however. That regulation and related restrictions on supply were found unconstitutional by the Federal Court of Canada in January, 2008. The court found that these regulations did not allow a sufficient legal supply of medical cannabis, and thus forced many patients to purchase their medicine from unauthorized, black market sources. This was the eighth time in the previous ten years that the courts ruled against Health Canada's regulations restricting the supply of the medicine.[181]

Reception desk at the Kingston Compassion Club Society [180] in Kingston, Ontario

In Canada there are four forms of medical cannabis. The first one is a cannabis extract called Sativex that contains THC and cannabidiol in a spray form. The second is a synthetic or manmade THC called dronabinol marketed as Marinol. The third also a synthetic version of THC called nabilone that is called Cesamet on the markets. The fourth product is the herbal form of cannabis often referred to as marijuana.[182]

Germany

In February 2008, seven German patients could legally be treated with medicinal cannabis, distributed by prescription in pharmacies.[183] To regulate therapeutic use, Germany modeled on Dutch neighbor who distributes this way since in 2003 (120 kg in 2008).

In Germany dronabinol was rescheduled in 1994 from annex I to annex II of the Narcotics Law (*Betäubungsmittelgesetz*) in order to ease research; in 1998 dronabinol was rescheduled from annex II to annex III and since then has been available by prescription,[184] whereas Δ^9-THC is still listed in annex I.[185] Manufacturing instructions for dronabinol containing compendial formulations are described in the *Neues Rezeptur-Formularium*.[173]

Israel

In modern history, the molecule THC was isolated in 1964 by Raphael Mechoulam and Yechiel Gaoni of the Weizmann Institute in Rehovot, Israel.

Medicine since 1999 recognized the prescription of therapeutic cannabis to cover the care according to the broadest scope of diseases for which there can be recognized: fibromyalgia, cancer, HIV / AIDS, neurological disorders, multiple sclerosis, of asthma and glaucoma, as well as post-traumatic stress.

An organization, originally with compassionate motives and a Hebrew concept of social justice, the Tikkun Olam, was officially presented in March 2007 the Ministry of Health as a leading provider of medical cannabis. In 2010, this concept is effective for patients from 4000 to 5000. This policy may predict an increase of up to 40,000 people by 2012.[186]

Netherlands

Since 2003, the country's pharmacies distribute medicinal cannabis (pharmaceutical form of the natural plant) by prescription, in addition to other drugs containing cannabinoids (dronabinol, Sativex).

Prescription medical cannabis in the Netherlands

The three therapeutic qualities produced by the company Bedrocan and distributed in the pharmacy are:

- Bedrocan (18% dronabinol / THC)
- Bediol (11% dronabinol / THC)
- Bedrobinol (6% + 7.5% CBD dronabinol).


Bedrocan


Bediol


Bedrobinol

The Office of Medicinal Cannabis (BMC), which reports to the Ministry of Health and Sports of the Netherlands, is responsible for ensuring control of the distribution of these new medicines.

In 2008, 120 kg of medical marijuana were sold through the network of pharmacies at a price of about 7 € / g.

Spain

In Spain, since the late 1990s and early 2000s, medical cannabis underwent a process of progressive decriminalization and legalisation. The parliament of the region of Catalonia was the first in Spain to have voted unanimously in 2001 legalizing medical marijuana; it was quickly followed by parliaments of Aragon and the Balearic Islands. The Spanish Penal Code prohibits the sale of cannabis but it does not prohibit consumption (although consumption on the street is fined). Until early 2000, the Penal Code did not distinguish between therapeutic use of cannabis and recreational use, however, several court decisions show that this distinction is increasingly taken into account by judges. From 2006, the sale of seed is legalized, the sale and public consumption remains illegal, and private cultivation and use are permitted.[187][188]

Several studies have been conducted to study the effects of cannabis on patients suffering from diseases like cancer, AIDS, multiple sclerosis, seizures or asthma. This research was conducted by various Spanish agencies at the Universidad Complutense de Madrid headed by Manuel Guzman, the hospital of La Laguna in Tenerife led neurosurgeon Luis González Feria or the University of Barcelona.

Several cannabis consumption clubs and user associations have been established throughout Spain. These clubs, the first of which was created in 1991, are non-profit associations who grow cannabis and sell it at cost to its members. The legal status of these clubs is uncertain: in 1997, four members of the first club, the Barcelona Ramón Santos Association of Cannabis Studies, were sentenced to 4 months in prison and a 3000 euro fine, while at about the same time, the court of Bilbao ruled that another club was not in violation of the law. The Andalusian regional government also commissioned a study by criminal law professors on the "Therapeutic use of cannabis and the creation of establishments of acquisition and consumption. The study concluded that such clubs are legal as long as they distribute only to a restricted list of legal adults, provide only the amount of drugs necessary for immediate consumption, and not earn a profit. The Andalusian government never formally accepted these guidelines and the

legal situation of the clubs remains insecure. In 2006 and 2007, members of these clubs were acquitted in trial for possession and sale of cannabis and the police were ordered to return seized crops.[188]

United Kingdom

In England and Wales, the use of cannabis medicinally is accepted as a mitigating factor under Sentencing Council guidelines, if it is being cultivated or found in possession of someone.[189] However, in the United Kingdom, possession of small quantities of cannabis does not usually warrant an arrest or court appearance (street cautions or fines are often given out instead). Under UK law, certain cannabinoids are permitted medically,[190] but these are strictly controlled with many provisos under the Misuse of Drugs Act 1971 (in the 1985 amendments). The British Medical Association's official stance is "users of cannabis for medical purposes should be aware of the risks, should enroll for clinical trials, and should talk to their doctors about new alternative treatments; but we do not advise them to stop."[190]

United States

In the United States federal level of government, cannabis *per se* has been made criminal by implementation of the Controlled Substances Act which classifies cannabis as a Schedule I drug, the strictest classification on par with heroin, LSD and ecstasy, and the Supreme Court ruled in 2005 that the Commerce Clause of the U.S. Constitution allowed the government to ban the use of cannabis, including medical use. The United States Food and Drug Administration states "marijuana has a high potential for abuse, has no currently accepted medical use in treatment in the United States, and has a lack of accepted safety for use under medical supervision".[191][192]

Medical Marijuana Dispensary

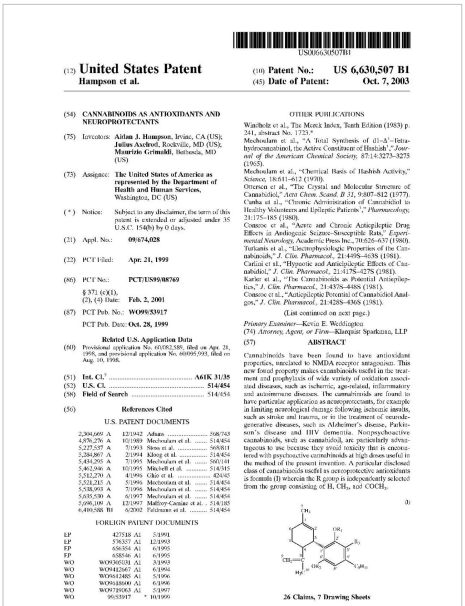
Only one American (for-profit) Company, Cannabis Science Inc., is working towards getting FDA approval for cannabis based medicines (including smoked cannabis). They want to have medical cannabis approved by the FDA so anyone, regardless of state, will have access to the medicine [193]. Also, there is one non-profit organization, the Multidisciplinary Association for Psychedelic Studies (MAPS) working towards getting Cannabis approved by the FDA for PTSD.

Since the medical marijuana movement commenced, and starting with California in 1996, nineteen states have legalized medical cannabis or effectively decriminalized it: Alaska,[194] Arizona,[195] California,[196] Colorado,[197] Connecticut,[198] [199] Delaware,[200][201] Hawaii,[202] Maine,[203] Michigan,[204] Montana,[205] Nevada,[206] New Jersey,[207] New Mexico,[208] Oregon,[209] Rhode Island,[210] Vermont,[211] Virginia,[212] Washington;[213] and Washington D.C.[214] Maryland allows for reduced or no penalties if cannabis use has a medical basis.[215][216][217] Despite its legality in Washington, and Michigan, an employee can still be fired if they test positive on a drug test, despite having a doctor's recommendation.[218] California, Colorado, New Mexico, Maine, Rhode Island, Montana, and Michigan are currently the only states to utilize dispensaries to sell medical cannabis. Connecticut will be the eighth but has yet to issue any licenses. California's medical cannabis industry took in about $2 billion a year and generated $100 million in state sales taxes during 2008[219] with an estimated 2,100 dispensaries, co-operatives, wellness clinics and taxi delivery services in the sector colloquially known as “cannabusiness”.[220]

On 19 October 2009 the US Deputy Attorney General issued a US Department of Justice memorandum to "All United States Attorneys" providing clarification and guidance to federal prosecutors in US States that have enacted laws authorizing the medical use of marijuana. The document is intended solely as "a guide to the exercise of investigative and prosecutorial discretion and as guidance on resource allocation and federal priorities." The US Deputy Attorney General David W. Ogden provided seven criteria, the application of which acts as a guideline to prosecutors and federal agents to ascertain whether a patients use, or their caregivers provision, of medical cannabis

"represents part of a recommended treatment regiment consistent with applicable state law", and recommends against prosecuting patients using medical cannabis products according to state laws. Not applying those criteria, the Dep. Attorney General Ogden concludes, would likely be "an inefficient use of limited federal resources". The memorandum does not change any laws. Sale of cannabis remains illegal under federal law.[221] The U.S. Food and Drug Administration's position, that marijuana has no accepted value in the treatment of any disease in the United States, has also remained the same.

The Health and Human Services Division of the federal government holds a patent US 6630507 [222] for medical cannabis. The patent, "Cannabinoids as antioxidants and neuroprotectants", issued October 2003[223] reads:



US006630507B1

(12) **United States Patent**
Hampson et al.

(10) **Patent No.: US 6,630,507 B1**
(45) **Date of Patent: Oct. 7, 2003**

(54) **CANNABINOIDS AS ANTIOXIDANTS AND NEUROPROTECTANTS**

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(73) Assignee: **The United States of America as represented by the Department of Health and Human Services**, Washington, DC (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/674,028**

(22) PCT Filed: **Apr. 21, 1999**

(86) PCT No.: **PCT/US99/08769**
§ 371 (c)(1),
(2), (4) Date: **Feb. 2, 2001**

(87) PCT Pub. No.: **WO99/53917**
PCT Pub. Date: **Oct. 28, 1999**

Related U.S. Application Data

(60) Provisional application No. 60/082,589, filed on Apr. 21, 1998, and provisional application No. 60/095,593, filed on Aug. 10, 1998.

(51) **Int. Cl.**[7] **A61K 31/35**
(52) **U.S. Cl.** **514/454**
(58) **Field of Search** 514/454

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(57) **ABSTRACT**

Cannabinoids have been found to have antioxidant properties, unrelated to NMDA receptor antagonism. This new found property makes cannabinoids useful in the treatment and prophylaxis of wide variety of oxidation associated diseases, such as ischemic, age-related, inflammatory and autoimmune diseases. The cannabinoids are found to have particular application as neuroprotectants, for example in limiting neurological damage following ischemic insults, such as stroke and trauma, or in the treatment of neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease and HIV dementia. Nonpsychoactive cannabinoids, such as cannabidiol, are particularly advantageous to use because they avoid toxicity that is encountered with psychoactive cannabinoids at high doses useful in the method of the present invention. A particular disclosed class of cannabinoids useful as neuroprotective antioxidants is formula (I) wherein the R group is independently selected from the group consisting of H, CH_3, and $COCH_3$.

(I)

26 Claims, 7 Drawing Sheets

The Health and Human Services Division of the Federal government of the United States holds a patent US 6630507 [222] for medical cannabis.

> Cannabinoids have been found to have antioxidant properties, unrelated to NMDA receptor antagonism. This new found property makes cannabinoids useful in the treatment and prophylaxis of wide variety of oxidation associated diseases, such as ischemic, age-related, inflammatory and autoimmune diseases. The cannabinoids are found to have particular application as neuroprotectants, for example in limiting neurological damage following ischemic insults, such as stroke and trauma, or in the treatment of neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease and HIV dementia... .[224]

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External links

- Medical Cannabis (http://www.theglobaldispatches.com/articles/medical-cannabis--3), article by Dr Tato Grasso in www.theglobaldispatches.com.
- Medical cannabis (http://www.dmoz.org/Society/Issues/Health/Drugs/Illegal/Pro-Legalization/Marijuana/Medical_Purposes//) at the Open Directory Project, links to websites about medical cannabis.
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- The Forbidden Medicine (http://www.rxmarijuana.com/), an independent site operated by Harvard Medical School faculty members James Bakalar and Lester Grinspoon.
- Cannabis Health Journal (http://www.cannabishealth.com/) Online Medicinal Marijuana magazine based in British Columbia.
- Medical Cannabis Information (http://kingstoncompassion.org/index.php/medical-cannabis-information) Online Medicinal Cannabis information database.

PubMed

PubMed

Content	
Contact	
Research center	United States National Library of Medicine (NLM)
Release date	January 1996
Access	
Website	www.ncbi.nlm.nih.gov/pubmed/ [1]
Tools	
Miscellaneous	

PubMed is a free database accessing primarily the MEDLINE database of references and abstracts on life sciences and biomedical topics. The United States National Library of Medicine (NLM) at the National Institutes of Health maintains the database as part of the Entrez information retrieval system. PubMed was first released in January 1996.[2]

Content

In addition to MEDLINE, PubMed provides access to:

- older references from the print version of *Index Medicus* back to 1951 and earlier;
- references to some journals before they were indexed in Index Medicus and MEDLINE, for instance *Science*, *BMJ*, and *Annals of Surgery*;
- very recent entries to records for an article before it is indexed with Medical Subject Headings (MeSH) and added to MEDLINE; and
- a collection of books available full-text and other subsets of NLM records.[3]

Many PubMed records contain links to full text articles, some of which are freely available, often in PubMed Central[4] and local mirrors such as UK PubMed Central.[5]

Information about the journals indexed in PubMed is found in the NLM Catalog.[6]

As of 20 September 2012, PubMed has over 22.1 million records going back to 1966, selectively to the year 1865, and *very* selectively to 1809; about 500,000 new records are added each year; 12.38 million of these articles are listed with their abstracts, and 12.81 million articles have links to full-text (of which 3.54 million articles are available full-text *for free* for any user). To see the current size of the database type "1800:2100[dp]" or "all[sb]" into the PubMed search window.[7]

Characteristics

Standard searches

Simple searches on PubMed can be carried out by entering key aspects of a subject into PubMed's search window.

PubMed translates this initial search formulation and automatically adds field names, relevant MeSH terms, synonyms, Boolean operators, and 'nests' the resulting terms appropriately, enhancing the search formulation significantly, in particular by routinely combining (using the OR operator) textwords and MeSH terms.

The examples given in a PubMed tutorial[8] demonstrate how this automatic process works:

> **Causes Sleep Walking** is translated as ("etiology"[Subheading] OR "etiology"[All Fields] OR "causes"[All Fields] OR "causality"[MeSH Terms] OR "causality"[All Fields]) **AND** ("somnambulism"[MeSH Terms] OR "somnambulism"[All Fields] OR ("sleep"[All Fields] AND "walking"[All Fields]) OR "sleep walking"[All Fields])

Likewise,

> **Heart Attack Aspirin Prevention** is translated as ("myocardial infarction"[MeSH Terms] OR ("myocardial"[All Fields] AND "infarction"[All Fields]) OR "myocardial infarction"[All Fields] OR ("heart"[All Fields] AND "attack"[All Fields]) OR "heart attack"[All Fields]) **AND** ("aspirin"[MeSH Terms] OR "aspirin"[All Fields]) **AND** ("prevention and control"[Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR "prevention"[All Fields])

The new PubMed interface, launched in October 2009, encourages the use of such quick, Google-like search formulations; they have also been described as 'telegram' searches.[9]

Comprehensive searches

For comprehensive, optimal searches in PubMed, it is necessary to have a thorough understanding of its core component, MEDLINE, and especially of the MeSH (Medical Subject Headings) controlled vocabulary used to index MEDLINE articles. They may also require complex search strategies, use of field names (tags), proper use of limits and other features, and are best carried out by PubMed search specialists or librarians,[10] who are able to select the right type of search and carefully adjust it for recall and precision.[11]

Clinical queries/systematic reviews

A special feature of PubMed is its "Clinical Queries" section, where "Clinical Categories", "Systematic Reviews", and "Medical Genetics" subjects can be searched, with study-type 'filters' automatically applied to identify substantial, robust studies.[12] As these 'clinical queries' can generate small sets of robust studies with considerable precision, it has been suggested that this PubMed section can be used as a 'point-of-care' resource.[13]

Related articles

A reference which is judged particularly relevant can be marked and "related articles" can be identified. If relevant, several studies can be selected and related articles to all of them can be generated (on PubMed or any of the other NCBI Entrez databases) using the 'Find related data' option. The related articles are then listed in order of "relatedness". To create these lists of related articles, PubMed compares words from the title and abstract of each citation, as well as the MeSH headings assigned, using a powerful word-weighted algorithm.[14] The 'related articles' function has been judged to be so precise that some researchers suggest it can be used instead of a full search.[15]

Mapping to MeSH headings and subheadings

A strong feature of PubMed is its ability to automatically link to MeSH terms and subheadings. Examples would be: "bad breath" links to (and includes in the search) "halitosis", "heart attack" to "myocardial infarction", "breast cancer" to "breast neoplasms". Where appropriate, these MeSH terms are automatically "expanded", that is, include more specific terms. Terms like "nursing" are automatically linked to "Nursing [MeSH]" or "Nursing [Subheading]". This important feature makes PubMed searches automatically more sensitive and avoids false-negative (missed) hits by compensating for the diversity of medical terminology.

My NCBI

The PubMed optional facility "My NCBI" (with free registration) provides tools for

- saving searches
- filtering search results
- setting up automatic updates sent by e-mail
- saving sets of references retrieved as part of a PubMed search
- configuring display formats or highlighting search terms

and a wide range of other options.[16] The "My NCBI" area can be accessed from any computer with web-access. An earlier version of "My NCBI" was called "PubMed Cubby".[17]

LinkOut

LinkOut, a NLM facility to link (and make available full-text) local journal holdings.[18] Some 3,200 sites (mainly academic institutions) participate in this NLM facility (as of March 2010), from Aalborg University in Denmark to ZymoGenetics in Seattle.[19] Users at these institutions see their institutions logo within the PubMed search result (if the journal is held at that institution) and can access the full-text.

PubMed for handhelds/mobiles

PubMed/MEDLINE can be accessed via handheld devices, using for instance the "PICO" option (for focused clinical questions) created by the NLM.[20] A "PubMed Mobile" option, providing access to a mobile friendly, simplified PubMed version, is also available.[21]

askMEDLINE

askMEDLINE, a free-text, natural language query tool for MEDLINE/PubMed, developed by the NLM, also suitable for handhelds.[22]

PubMed identifier

A **PMID** (PubMed identifier or PubMed unique identifier)[23] is a unique number assigned to each PubMed record.

The assignment of a PMID or PMCID to a publication tells the reader nothing about the type or quality of the content. PMIDs are assigned to letters to the editor, editorial opinions, op-ed columns, and any other piece that the editor chooses to include in the journal, as well as peer-reviewed papers. The existence of the identification number is also not proof that the papers have not been retracted for fraud, incompetence, or misconduct. The announcement about any corrections to original papers may be assigned a PMID.

Alternative interfaces

The National Library of Medicine leases the MEDLINE information to a number of private vendors such as Ovid, Dialog, EBSCO, Knowledge Finder and many other commercial, non-commercial, and academic providers.[24] As of October 2008, more than 500 licences had been issued, more than 200 of them to non-US providers. As licences to use MEDLINE data are available for free, the NLM in effect provides a free testing ground for a wide range[25] of alternative interfaces and 3rd party additions to PubMed, one of a very few large, professionally curated databases which offers this option.

Lu [25] identifies a sample of 28 current and free web based PubMed versions, requiring no installation or registration, which are grouped into four categories:

- Ranking search results, for instance: eTBLAST; Hakia; MedlineRanker;[26] MiSearch;[27]
- Clustering results by topics, authors, journals etc., for instance: Anne O'Tate;[28] ClusterMed;[29]
- Enhancing semantics and visualisation, for instance: CiteXplore; EBIMed;[30] MedEvi;[31]
- Improved search interface and retrieval experience, for instance: askMEDLINE;[32][33] BabelMeSH;[34]PubCrawler;[35]

As most of these and other alternatives rely essentially on PubMed/MEDLINE data leased under license from the NLM/PubMed, the term "PubMed derivatives" has been suggested.[25]

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Cannabinoid

Cannabinoids are a class of diverse chemical compounds that activate cannabinoid receptors. These include the endocannabinoids (produced naturally in the body by humans and animals),[1] the phytocannabinoids(found in cannabis and some other plants), and synthetic cannabinoids (produced chemically by humans). The most notable cannabinoid is the phytocannabinoid Δ^9-tetrahydrocannabinol (THC), the primary psychoactive compound of cannabis.[2][3] However, there are known to exist numerous other cannabinoids with varied effects.

Synthetic cannabinoids encompass a variety of distinct chemical classes: the classical cannabinoids structurally related to THC, the nonclassical cannabinoids (cannabimimetics) including the aminoalkylindoles, 1,5-diarylpyrazoles, quinolines, and arylsulphonamides, as well as eicosanoids related to the endocannabinoids.[2]

Cannabinoid receptors

Before the 1980s, it was often speculated that cannabinoids produced their physiological and behavioral effects via nonspecific interaction with cell membranes, instead of interacting with specific membrane-bound receptors. The discovery of the first cannabinoid receptors in the 1980s helped to resolve this debate. These receptors are common in animals, and have been found in mammals, birds, fish, and reptiles. At present, there are two known types of cannabinoid receptors, termed CB_1 and CB_2,[1] with mounting evidence of more.[4] The human brain has more cannabinoid receptors than any other GPCR type.[5]

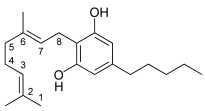
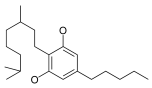
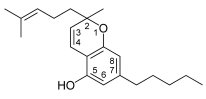
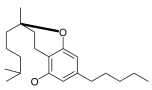
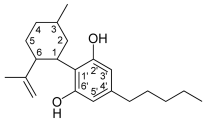
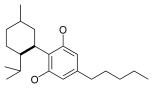
Cannabinoid receptor type 1

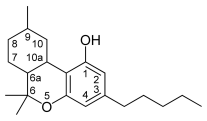
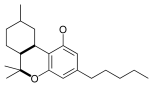
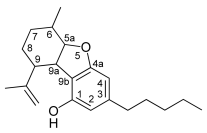
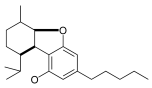
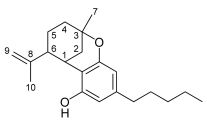
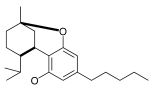
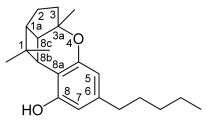
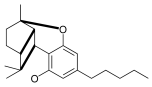
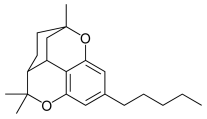
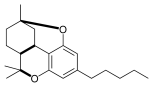
CB_1 receptors are found primarily in the brain, to be specific in the basal ganglia and in the limbic system, including the hippocampus.[1] They are also found in the cerebellum and in both male and female reproductive systems. CB_1 receptors are absent in the medulla oblongata, the part of the brain stem responsible for respiratory and cardiovascular functions. Thus, there is not the risk of respiratory or cardiovascular failure that can be produced by some drugs. CB_1 receptors appear to be responsible for the euphoric and anticonvulsive effects of cannabis.

Cannabinoid receptor type 2

CB_2 receptors are predominantly found in the immune system, or immune-derived cells[6] with the greatest density in the spleen. While found only in the peripheral nervous system, a report does indicate that CB_2 is expressed by a subpopulation of microglia in the human cerebellum .[7] CB_2 receptors appear to be responsible for the anti-inflammatory and possibly other therapeutic effects of cannabis.[6]

Phytocannabinoids

Type	Skeleton	Cyclization
Cannabigerol-type **CBG**		
Cannabichromene-type **CBC**		
Cannabidiol-type **CBD**		

Tetrahydrocannabinol- and Cannabinol-type **THC, CBN**		
Cannabielsoin-type **CBE**		
iso-Tetrahydrocannabinol-type ***iso*-THC**		
Cannabicyclol-type **CBL**		
Cannabicitran-type **CBT**		
Main classes of natural cannabinoids		

Phytocannabinoids (also called *natural cannabinoids*, *herbal cannabinoids*, and *classical cannabinoids*) are known to occur in several different plant species. These include *Cannabis sativa*, *Cannabis indica*, *Echinacea purpurea*, *Echinacea angustifolia*, *Echinacea pallida*, *Acmella oleracea*, *Helichrysum umbraculigerum*, and *Radula marginata*.[8] The best known herbal cannabinoids are Δ9-tetrahydrocannabinol (THC) from *Cannabis* and the lipophilic alkamides (alkylamides) from *Echinacea* species.[8]

A significant number of cannabinoids are found in both *Cannabis* and *Echinacea* plants. In *Cannabis*, these cannabinoids are concentrated in a viscous resin produced in structures known as glandular trichomes. In *Echinacea* species, cannabinoids are found throughout the plant structure, but are most concentrated in the roots and stems.[9] Tea (Camellia sinensis) catechins have an affinity for human cannabinoid receptors.[10]

Phytocannabinoids are nearly insoluble in water but are soluble in lipids, alcohols, and other non-polar organic solvents. However, as phenols, they form more water-soluble phenolate salts under strongly alkaline conditions.

All-natural cannabinoids are derived from their respective 2-carboxylic acids (2-COOH) by decarboxylation (catalyzed by heat, light, or alkaline conditions).

Types

At least 85 different cannabinoids have been isolated from the *Cannabis* plant.[11] At least 25 different cannabinoids have been isolated from *Echinacea* species.[12] To the right, the main classes of cannabinoids from *Cannabis* are shown. All classes derive from cannabigerol-type compounds and differ mainly in the way this precursor is cyclized.

Tetrahydrocannabinol (THC), cannabidiol (CBD), cannabinol (CBN), and Dodeca-2E,4E,8Z,10E/Z-tetraenoic-acid-isobutylamides (from *Echinacea* species) are the most prevalent natural cannabinoids and have received the most study. Other common cannabinoids are listed below:

- CBG (Cannabigerol)
- CBC (Cannabichromene)
- CBL (Cannabicyclol)
- CBV (Cannabivarin)
- THCV (Tetrahydrocannabivarin)

- CBDV (Cannabidivarin)
- CBCV (Cannabichromevarin)
- CBGV (Cannabigerovarin)
- CBGM (Cannabigerol Monomethyl Ether)

Tetrahydrocannabinol

Tetrahydrocannabinol (THC) is the primary psychoactive component of the plant. It appears to ease moderate pain (analgesic) and to be neuroprotective. THC has approximately equal affinity for the CB_1 and CB_2 receptors.[13]

Delta-9-Tetrahydrocannabinol (Δ^9-THC, THC) and *delta*-8-tetrahydrocannabinol (Δ^8-THC), mimic the action of anandamide, a neurotransmitter produced naturally in the body. These two THC's produce the effects associated with cannabis by binding to the CB_1 cannabinoid receptors in the brain.

Cannabidiol

Cannabidiol (CBD) is not particularly psychoactive in and of itself, and was thought not to affect the psychoactivity of THC.[14] However, recent evidence shows that smokers of cannabis with a higher CBD/THC ratio were less likely to experience schizophrenia-like symptoms.[15] This is supported by psychological tests, in which participants experience less intense psychotic-like effects when intravenous THC was co-administered with CBD (as measured with a PANSS test).[16] Cannabidiol has little affinity for CB_1 and CB_2 receptors but acts as an indirect antagonist of cannabinoid agonists.[17] Recently it was found to be an antagonist at the putative new cannabinoid receptor, GPR55, a GPCR expressed in the caudate nucleus and putamen.[18] Cannabidiol has also been shown to act as a $5\text{-}HT_{1A}$ receptor agonist,[19] an action that is involved in its antidepressant,[20][21] anxiolytic,[21][22] and neuroprotective[23][24] effects.

It appears to relieve convulsion, inflammation, anxiety, and nausea.[25] CBD has a greater affinity for the CB_2 receptor than for the CB_1 receptor.[25]

CBD shares a precursor with THC and is the main cannabinoid in low-THC *Cannabis* strains. CBD apparently plays a role in preventing the short-term memory loss associated with THC in mammals.

Cannabinol

Cannabinol (CBN) is the primary product of THC degradation, and there is usually little of it in a fresh plant. CBN content increases as THC degrades in storage, and with exposure to light and air. It is only mildly psychoactive. Its affinity to the CB_2 receptor is higher than for the CB_1 receptor.[26]

Cannabigerol

Cannabigerol (CBG) is non-psychotomimetic but still affects the overall effects of Cannabis. It acts as an α_2-adrenergic receptor agonist, $5\text{-}HT_{1A}$ receptor antagonist, and CB_1 receptor antagonist.[27] It also binds to the CB_2 receptor.[27]

Tetrahydrocannabivarin

Tetrahydrocannabivarin (THCV) is prevalent in certain central Asian and southern African strains of *Cannabis*.[28][29] It is an antagonist of THC at CB_1 receptors and attenuates the psychoactive effects of THC.[30]

Cannabidivarin

Although cannabidivarin (CBDV) is usually a minor constituent of the cannabinoid profile, enhanced levels of CBDV have been reported in feral plants from the northwest Himalayas, and in hashish from Nepal.[31][29]

Cannabichromene

Cannabichromene (CBC) is non-psychoactive and does not affect the psychoactivity of THC .[14]

Double bond position

In addition, each of the compounds above may be in different forms depending on the position of the double bond in the alicyclic carbon ring. There is potential for confusion because there are different numbering systems used to describe the position of this double bond. Under the dibenzopyran numbering system widely used today, the major form of THC is called Δ^9-THC, while the minor form is called Δ^8-THC. Under the alternate terpene numbering system, these same compounds are called Δ^1-THC and Δ^6-THC, respectively.

Length

Most herbal cannabinoid compounds are 21-carbon compounds. However, some do not follow this rule, primarily because of variation in the length of the side-chain attached to the aromatic ring. In THC, CBD, and CBN, this side-chain is a pentyl (5-carbon) chain. In the most common homologue, the pentyl chain is replaced with a propyl (3-carbon) chain. Cannabinoids with the propyl side-chain are named using the suffix *varin*, and are designated, for example, THCV, CBDV, or CBNV.

Plant profile

Cannabis plants can exhibit wide variation in the quantity and type of cannabinoids they produce. The mixture of cannabinoids produced by a plant is known as the plant's cannabinoid profile. Selective breeding has been used to control the genetics of plants and modify the cannabinoid profile. For example, strains that are used as fiber (commonly called hemp) are bred such that they are low in psychoactive chemicals like THC. Strains used in medicine are often bred for high CBD content, and strains used for recreational purposes are usually bred for high THC content or for a specific chemical balance.

Quantitative analysis of a plant's cannabinoid profile is often determined by gas chromatography (GC), or more reliably by gas chromatography combined with mass spectrometry (GC/MS). Liquid chromatography (LC) techniques are also possible, and, unlike GC methods, can differentiate between the acid and neutral forms of the cannabinoids. There have been systematic attempts to monitor the cannabinoid profile of cannabis over time, but their accuracy is impeded by the illegal status of the plant in many countries.

Pharmacology

Cannabinoids can be administered by smoking, vaporizing, oral ingestion, transdermal patch, intravenous injection, sublingual absorption, or rectal suppository. Once in the body, most cannabinoids are metabolized in the liver, especially by cytochrome P450 mixed-function oxidases, mainly CYP 2C9. Thus supplementing with CYP 2C9 inhibitors leads to extended intoxication.

Some is also stored in fat in addition to being metabolized in liver. Δ^9-THC is metabolized to 11-hydroxy-Δ^9-THC, which is then metabolized to 9-carboxy-THC. Some cannabis metabolites can be detected in the body several weeks after administration. These metabolites are the chemicals recognized by common antibody-based "drug tests"; in the case of THC et al., these loads do not represent intoxication (compare to ethanol breath tests that measure instantaneous blood alcohol levels) but an integration of past consumption over an approximately month-long window.

Plant synthesis

Cannabinoid production starts when an enzyme causes geranyl pyrophosphate and olivetolic acid to combine and form CBG. Next, CBG is independently converted to either CBD or CBC by two separate synthase enzymes. CBD is then enzymatically cyclized to THC. For the propyl homologues (THCV, CBDV and CBNV), there is a similar pathway that is based on CBGV. Recent studies show that THC is not cyclized from CBD but rather directly from CBG. No experiment thus far has turned up an enzyme that converts CBD into THC, although it is still hypothesized.

Separation

Cannabinoids can be separated from the plant by extraction with organic solvents. Hydrocarbons and alcohols are often used as solvents. However, these solvents are flammable and many are toxic. Butane may be used, which evaporates extremely quickly. Supercritical solvent extraction with carbon dioxide is an alternative technique. Although this process requires high pressures (73 atmospheres or more), there is minimal risk of fire or toxicity, solvent removal is simple and efficient, and extract quality can be well controlled. Once extracted, cannabinoid blends can be separated into individual components using wiped film vacuum distillation or other distillation techniques. However, to produce high-purity cannabinoids, chemical synthesis or semisynthesis is generally required.

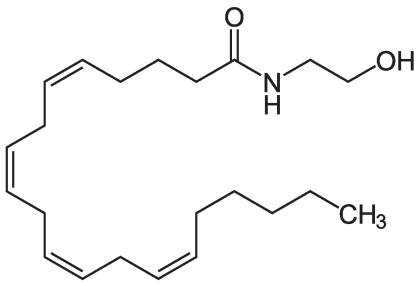
History

Cannabinoids were first discovered in the 1940s, when CBD and CBN were identified. The structure of THC was first determined in 1964.

Due to molecular similarity and ease of synthetic conversion, CBD was originally believed to be a natural precursor to THC. However, it is now known that CBD and THC are produced independently in the cannabis plant from the precursor CBG.

Endocannabinoids

Endocannabinoids are substances produced from within the body that activate cannabinoid receptors. After the discovery of the first cannabinoid receptor in 1988, scientists began searching for an endogenous ligand for the receptor.



Anandamide, an endogenous ligand of CB_1 and CB_2

Types of endocannabinoid ligands

- Arachidonoylethanolamine (Anandamide or AEA)

In 1992, in Raphael Mechoulam's lab, the first such compound was identified as arachidonoyl ethanolamine and named anandamide, a name derived from the Sanskrit word for bliss and *-amide*. Anandamide is derived from the essential fatty acid arachidonic acid. It has a pharmacology similar to THC, although its chemical structure is different. Anandamide binds to the central (CB_1) and, to a lesser extent, peripheral (CB_2) cannabinoid receptors, where it acts as a partial agonist. Anandamide is about as potent as THC at the CB_1 receptor.[32] Anandamide is found in nearly all tissues in a wide range of animals.[33] Anandamide has also been found in plants, including small amounts in chocolate.[34]

Two analogs of anandamide, 7,10,13,16-docosatetraenoylethanolamide and *homo*-γ-linolenoylethanolamine, have similar pharmacology. All of these are members of a family of signalling lipids called *N*-acylethanolamines, which also includes the noncannabimimetic palmitoylethanolamide and oleoylethanolamide, which possess anti-inflammatory and orexigenic effects, respectively. Many *N*-acylethanolamines have also been identified in plant seeds[35] and in molluscs.[36]

- 2-arachidonoyl glycerol (2-AG)

Another endocannabinoid, 2-arachidonoyl glycerol, binds to both the CB_1 and CB_2 receptors with similar affinity, acting as a full agonist at both.[32] 2-AG is present at significantly higher concentrations in the brain than anandamide,[37] and there is some controversy over whether 2-AG rather than anandamide is chiefly responsible for endocannabinoid signalling *in vivo*.[38] In particular, one *in vitro* study suggests that 2-AG is capable of stimulating higher G-protein activation than anandamide, although the physiological implications of this finding are not yet known.[39]

- 2-arachidonyl glyceryl ether (noladin ether)

In 2001, a third, ether-type endocannabinoid, 2-arachidonyl glyceryl ether (noladin ether), was isolated from porcine brain.[40] Prior to this discovery, it had been synthesized as a stable analog of 2-AG; indeed, some controversy remains over its classification as an endocannabinoid, as another group failed to detect the substance at "any appreciable amount" in the brains of several different mammalian species.[41] It binds to the CB_1 cannabinoid receptor (K_i = 21.2 nmol/L) and causes sedation, hypothermia, intestinal immobility, and mild antinociception in mice. It binds primarily to the CB_1 receptor, and only weakly to the CB_2 receptor.[32]

- N-arachidonoyl-dopamine (NADA)

Discovered in 2000, NADA preferentially binds to the CB_1 receptor.[42] Like anandamide, NADA is also an agonist for the vanilloid receptor subtype 1 (TRPV1), a member of the vanilloid receptor family.[43][44]

- Virodhamine (OAE)

A fifth endocannabinoid, virodhamine, or *O*-arachidonoyl-ethanolamine (OAE), was discovered in June 2002. Although it is a full agonist at CB_2 and a partial agonist at CB_1, it behaves as a CB_1 antagonist *in vivo*. In rats, virodhamine was found to be present at comparable or slightly lower concentrations than anandamide in the brain, but 2- to 9-fold higher concentrations peripherally.[45]

Function

Endocannabinoids serve as intercellular 'lipid messengers', signaling molecules that are released from one cell and activating the cannabinoid receptors present on other nearby cells. Although in this intercellular signaling role they are similar to the well-known monoamine neurotransmitters, such as acetylcholine and dopamine, endocannabinoids differ in numerous ways from them. For instance, they use retrograde signaling. Furthermore, endocannabinoids are lipophilic molecules that are not very soluble in water. They are not stored in vesicles, and exist as integral constituents of the membrane bilayers that make up cells. They are believed to be synthesized 'on-demand' rather than made and stored for later use. The mechanisms and enzymes underlying the biosynthesis of endocannabinoids remain elusive and continue to be an area of active research.

The endocannabinoid 2-AG has been found in bovine and human maternal milk.[46]

Retrograde signal

Conventional neurotransmitters are released from a 'presynaptic' cell and activate appropriate receptors on a 'postsynaptic' cell, where presynaptic and postsynaptic designate the sending and receiving sides of a synapse, respectively. Endocannabinoids, on the other hand, are described as retrograde transmitters because they most commonly travel 'backward' against the usual synaptic transmitter flow. They are, in effect, released from the postsynaptic cell and act on the presynaptic cell, where the target receptors are densely concentrated on axonal terminals in the zones from which conventional neurotransmitters are released. Activation of cannabinoid receptors temporarily reduces the amount of conventional neurotransmitter released. This endocannabinoid mediated system permits the postsynaptic cell to control its own incoming synaptic traffic. The ultimate effect on the endocannabinoid-releasing cell depends on the nature of the conventional transmitter being controlled. For instance, when the release of the inhibitory transmitter GABA is reduced, the net effect is an increase in the excitability of the endocannabinoid-releasing cell. On the converse, when release of the excitatory neurotransmitter glutamate is reduced, the net effect is a decrease in the excitability of the endocannabinoid-releasing cell.

Range

Endocannabinoids are hydrophobic molecules. They cannot travel unaided for long distances in the aqueous medium surrounding the cells from which they are released, and therefore act locally on nearby target cells. Hence, although emanating diffusely from their source cells, they have much more restricted spheres of influence than do hormones, which can affect cells throughout the body.

U.S. Patent no. 6630507

On October 7, 2003, a U.S. patent number 6630507 entitled "Cannabinoids as Antioxidants and Neuroprotectants" was awarded to the United States Department of Health and Human Services, based on research done at the National Institute of Mental Health (NIMH), and the National Institute of Neurological Disorders and Stroke (NINDS). This patent claims that cannabinoids are "useful in the treatment and prophylaxis of wide variety of oxidation associated diseases such as ischemia, age-related, inflammatory, and autoimmune diseases. The cannabinoids are found to have particular application as neuroprotectants, for example in limiting neurological damage following ischemic insults, such as stroke and trauma, or in the treatment of neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease and HIV dementia."[47][48]

On November 17, 2011, in accordance with 35 U.S.C. 209(c)(1) and 37 CFR part 404.7(a)(1)(i), the National Institutes of Health, Department of Health and Human Services, published in the Federal Register, that it is contemplating the grant of an exclusive patent license to practice the invention embodied in U.S. Patent 6,630,507, entitled "Cannabinoids as antioxidants and neuroprotectants" and PCT Application Serial No. PCT/US99/08769 and foreign equivalents thereof, entitled "Cannabinoids as antioxidants and neuroprotectants" [HHS Ref. No. E-287-1997/2] to KannaLife Sciences Inc., which has offices in New York, U.S. This patent and its foreign

counterparts have been assigned to the Government of the United States of America. The prospective exclusive license territory may be worldwide, and the field of use may be limited to: The development and sale of cannabinoid(s) and cannabidiol(s) based therapeutics as antioxidants and neuroprotectants for use and delivery in humans, for the treatment of hepatic encephalopathy, as claimed in the Licensed Patent Rights.[49]

On June 12, 2012, KannaLife Sciences, Inc. signed an exclusive license agreement with National Institutes of Health – Office of Technology Transfer ("NIH-OTT") for the Commercialization of U.S. Patent 6,630,507, "Cannabinoids as Antioxidants and Neuroprotectants" (the "'507 Patent"). The '507 Patent includes among other things, claims directed to a method of treating diseases caused by oxidative stress by administering a therapeutically effective amount of a non-psychoactive cannabinoid that has substantially no binding to the NMDA receptor. Cannabinoids are any of a group of related compounds that include cannabinol and the active constituents of cannabis (marijuana).</ref>

Synthetic and patented cannabinoids

Historically, laboratory synthesis of cannabinoids were often based on the structure of herbal cannabinoids, and a large number of analogs have been produced and tested, especially in a group led by Roger Adams as early as 1941 and later in a group led by Raphael Mechoulam. Newer compounds are no longer related to natural cannabinoids or are based on the structure of the endogenous cannabinoids.

Synthetic cannabinoids are particularly useful in experiments to determine the relationship between the structure and activity of cannabinoid compounds, by making systematic, incremental modifications of cannabinoid molecules.

Medications containing natural or synthetic cannabinoids or cannabinoid analogs:

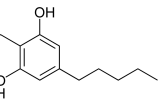
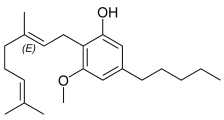
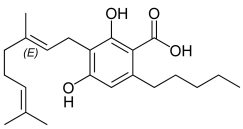
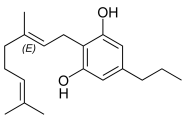
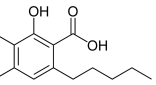
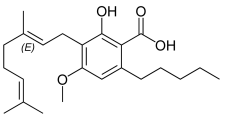
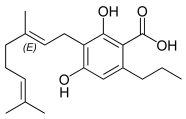
- Dronabinol (Marinol), is Δ^9-tetrahydrocannabinol (THC), used as an appetite stimulant, anti-emetic, and analgesic
- Nabilone (Cesamet), a synthetic cannabinoid and an analog of Marinol. It is Schedule II unlike Marinol, which is Schedule III
- Sativex, a cannabinoid extract oral spray containing THC, CBD, and other cannabinoids used for neuropathic pain and spasticity in 22 countries including England, Canada and Spain. Sativex develops whole-plant cannabinoid medicines
- Rimonabant (SR141716), a selective cannabinoid (CB_1) receptor inverse agonist used as an anti-obesity drug under the proprietary name Acomplia. It is also used for smoking cessation

Other notable synthetic cannabinoids include:

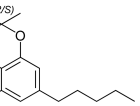
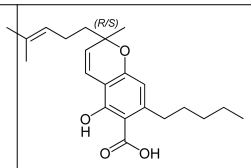
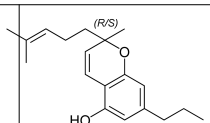
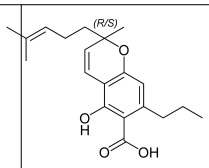
- JWH-018, a potent synthetic cannabinoid agonist discovered by Dr. John W. Huffman at Clemson University. It is being increasingly sold in legal smoke blends collectively known as "spice". Several countries and states have moved to ban it legally.
- CP-55940, produced in 1974, this synthetic cannabinoid receptor agonist is many times more potent than THC.
- Dimethylheptylpyran
- HU-210, about 100 times as potent as THC[50]
- HU-331 a potential anti-cancer drug derived from cannabidiol that specifically inhibits topoisomerase II.
- SR144528, a CB_2 receptor antagonist
- WIN 55,212-2, a potent cannabinoid receptor agonist
- JWH-133, a potent selective CB_2 receptor agonist
- Levonantradol (Nantrodolum), an anti-emetic and analgesic but not currently in use in medicine
- AM-2201, a potent cannabinoid receptor agonist.

Table of natural cannabinoids

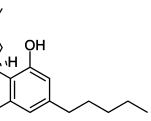
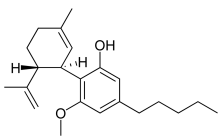
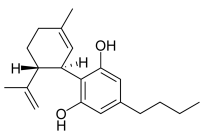
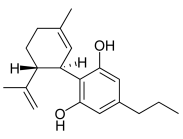
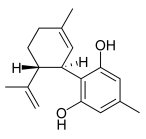
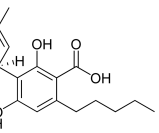
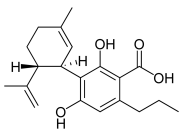
Cannabigerol-type (CBG)

 Cannabigerol **(*E*)-CBG-C_5**	 Cannabigerol monomethyl ether **(*E*)-CBGM-C_5 A**	 Cannabinerolic acid A **(Z)-CBGA-C_5 A**	 Cannabigerovarin **(*E*)-CBGV-C_3**	
 Cannabigerolic acid A **(*E*)-CBGA-C_5 A**	 Cannabigerolic acid A monomethyl ether **(*E*)-CBGAM-C_5 A**	 Cannabigerovarinic acid A **(*E*)-CBGVA-C_3 A**		

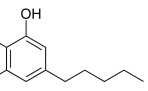
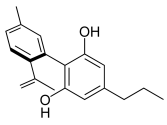
Cannabichromene-type (CBC)

 (±)-Cannabichr **CBC-C_5**	 (±)-Cannabichromenic acid A **CBCA-C_5 A**	 (±)-Cannabivarichro (±)-Cannabichromevarin **CBCV-C_3**	 (±)-Cannabichromevarinic acid A **CBCVA-C_3 A**	

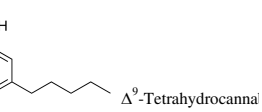
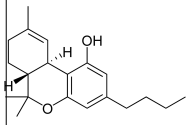
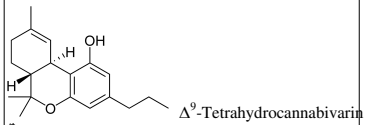
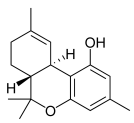
Cannabidiol-type (CBD)

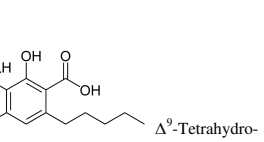
 (−)-Cannabidiol **CBD-C_5**	 Cannabidiol momomethyl ether **CBDM-C_5**	 Cannabidiol-C_4 **CBD-C_4**	 (−)-Cannabidivarin **CBDV-C_3**	 Cannabi **CBD-C_1**
 Cannabidiolic acid **CBDA-C_5**	 Cannabidivarinic acid **CBDVA-C_3**			

Cannabinodiol-type (CBND)

 Cannabinodiol **CBND-C_5**	 Cannabinodivarin **CBND-C_3**			

Tetrahydrocannabinol-type (THC)

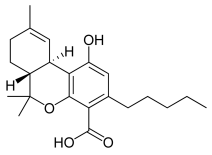
 Δ^9-Tetrahydrocanna **Δ^9-THC-C_5**	 Δ^9-Tetrahydrocannabinol- **Δ^9-THC-C_4**	 Δ^9-Tetrahydrocannabivarin **Δ^9-THCV-C_3**	 Δ^9-Tetrahydrocannabiorcol **Δ^9-THCO-C_1**	



Δ^9-Tetrahydro-

cannabinolic acid A

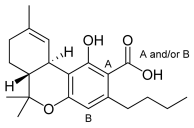
Δ^9-THCA-C_5 A



Δ^9-Tetrahydro-

cannabinolic acid B

Δ^9-THCA-C_5 B

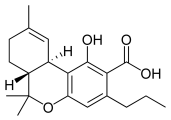


Δ^9-Tetrahydro-

cannabinolic acid-C_4

A and/or B

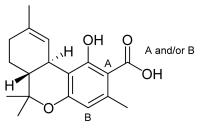
Δ^9-THCA-C_4 A and/or B



Δ^9-Tetrahydro-

cannabivarinic acid A

Δ^9-THCVA-C_3 A

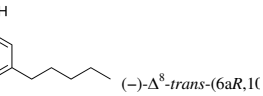


Δ^9-T

cannabiorcolic acid

A and/or B

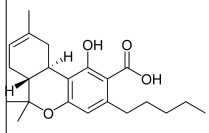
Δ^9-THCOA-C_1 A and/or



(−)-Δ^8-*trans*-(6a*R*,1(

Δ^8-Tetrahydrocannabinol

Δ^8-THC-C_5

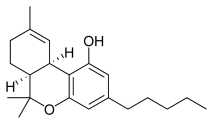


(−)-Δ^8-*trans*-(6a*R*,10a*R*)

Tetrahydrocannabinolic

acid A

Δ^8-THCA-C_5 A

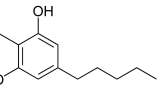


(−)-(6a*S*,10a*R*)-Δ^9-

Tetrahydrocannabinol

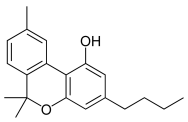
(−)-*cis*-Δ^9-THC-C_5

Cannabinol-type (CBN)



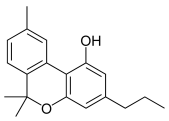
Cannabinol

CBN-C_5



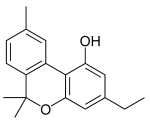
Cannabinol-C_4

CBN-C_4



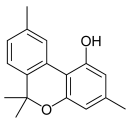
Cannabivarin

CBN-C_3



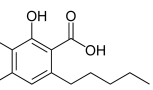
Cannabinol-C_2

CBN-C_2



Cannabi

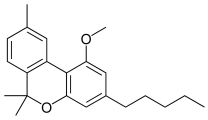
CBN-C_1



Cannabinolic

acid A

CBNA-C_5 A

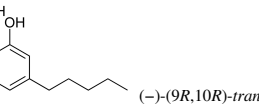


Cannabinol methyl

ether

CBNM-C_5

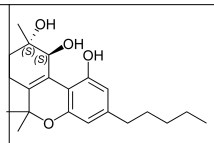
Cannabitriol-type (CBT)



(−)-(9*R*,10*R*)-*tran*

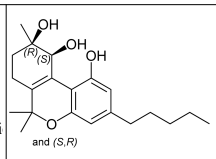
Cannabitriol

(−)-*trans*-CBT-C_5



(+)-(9*S*,10*S*)-Cannabitri

(+)-*trans*-CBT-C_5

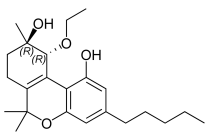


and (*S*,*R*)

(±)-(9*R*,10*S*/9*S*,10*R*)-

Cannabitriol

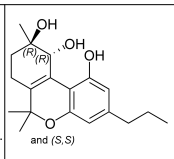
(±)-*cis*-CBT-C_5



(−)-(9*R*,10*R*)-*trans*-

10-O-Ethyl-cannabitriol

(−)-*trans*-CBT-OEt-C_5

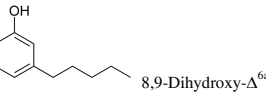


and (*S*,*S*)

(±)-(9*R*,10

Cannabitriol-C_3

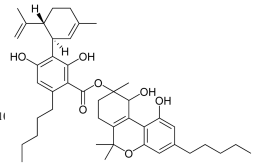
(±)-*trans*-CBT-C_3



8,9-Dihydroxy-$\Delta^{6a(10}$

tetrahydrocannabinol

8,9-Di-OH-CBT-C_5

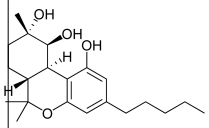


Cannabidiolic

acid A

cannabitriol ester

CBDA-C_5 9-OH-CBT-C_5 ester



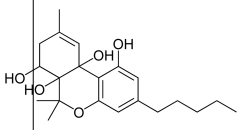
(−)-(6a*R*,9*S*,10*S*,

9,10-Dihydroxy-

hexahydrocannabinol,

Cannabiripsol

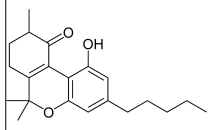
Cannabiripsol-C_5



(−)-6a,7,10a-Trihyd

Δ^9-tetrahydrocannabinol

(−)-Cannabitetrol

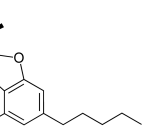


10-(

tetrahydrocannabinol

OTHC

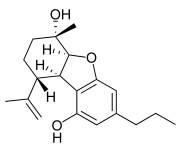
Cannabielsoin-type (CBE)



(5a*S*,6*S*,9*R*,9a*R*)-

Cannabielsoin

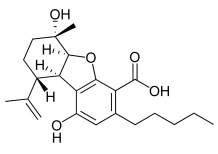
CBE-C_5



(5a*S*,6*S*,9*R*,9a*R*)-

C_3-Cannabielsoin

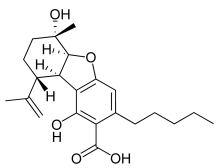
CBE-C_3



(5a*S*,6*S*,9*R*,9a*R*)-

Cannabielsoic acid A

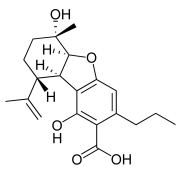
CBEA-C_5 A



(5a*S*,6*S*,9*R*,9a*R*)-

Cannabielsoic acid B

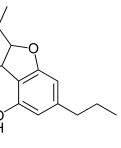
CBEA-C_5 B



(5a*S*,6*S*

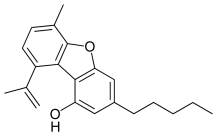
C_3-Cannabielsoic acid B

CBEA-C_3 B



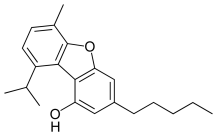
Cannabiglendol-C_3

OH-iso-HHCV-C_3



Dehydrocannabifuran

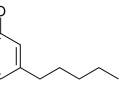
DCBF-C_5



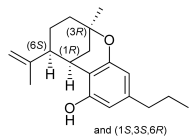
Cannabifuran

CBF-C_5

Isocannabinoids

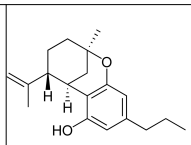


(−)-Δ^7-*trans*-(1*R*,3*R*,6*R*)-Isotetrahydrocannabinol



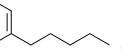
and (1*S*,3*S*,6*R*)

(±)-Δ^7-1,2-*cis*-(1*R*,3*R*,6*S*/1*S*,3*S*,6*R*)-Isotetrahydrocannabivarin



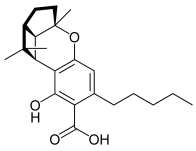
(−)-Δ^7-*trans*-(1*R*,3*R*,6*R*)-Isotetrahydrocannabivarin

Cannabicyclol-type (CBL)



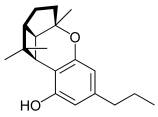
(±)-(1a*S*,3a*R*,8b*R*,8c*R*)-Cannabicyclol

CBL-C_5



(±)-(1a*S*,3a*R*,8b*R*,8c*R*)-Cannabicyclolic acid A

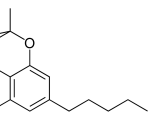
CBLA-C_5 A



(±)-(1a*S*,3a*R*,8b*R*,8c*R*)-Cannabicyclovarin

CBLV-C_3

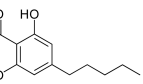
Cannabicitran-type (CBT)



Cannabicitran

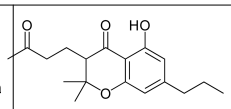
CBT-C_5

Cannabichromanone-type (CBCN)



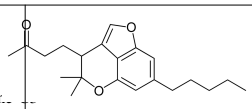
Cannabichroma

CBCN-C_5



Cannabichromanor...

CBCN-C_3



Cannabicoumaronone

CBCON-C_5

Natural occurrence

Cannabis indica may have a CBD:THC ratio 4–5 times that of *Cannabis sativa*. Cannabis strains with relatively high CBD:THC ratios are less likely to induce anxiety than vice versa. This may be due to CBD's antagonistic effects at the cannabinoid receptors, compared to THC's partial agonist effect. CBD is also a 5-HT_{1A} receptor agonist, which may also contribute to an anxiolytic effect.[51] This likely means the high concentrations of CBD found in *Cannabis indica* mitigate the anxiogenic effect of THC significantly.[51] The effects of *sativa* are well known for its cerebral high, hence used daytime as medical cannabis, while *indica* are well known for its sedative effects and preferred night time as medical cannabis.[51]

References

The bud of a *Cannabis indica* flower coated with trichomes, which may contain 4-5 times more CBD than *Cannabis sativa*

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External links

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- Chemical Ecology of Cannabis (J. Intl. Hemp Assn. - 1994) (http://www.hempfood.com/IHA/iha01201.html)
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Cannabinoid research organizations

- The International Cannabinoid Research Society (http://www.cannabinoidsociety.org)
- The Canadian Consortium for the Investigation of Cannabinoids (http://www.ccic.net)
- Therapeutic Potential in Spotlight at Cannabinoid Researchers' Meeting (http://www.ccrmg.org/journal/04spr/potential.html) at California Cannabis Research Medical Group
- International Cannabinoid Research Society (http://cannabinoidsociety.org/)

Cannabis Science Inc.

Cannabis Science Inc. is a start-up biotech company based in Colorado Springs, CO. Cannabis Science was incorporated in 2009 and trades publicly under the ticker CBIS on the Over-The-Counter Bulletin Board (OTCBB:CBIS)[1]. Their goal is to get Cannabis based medicines approved by the FDA, with current focus on Skin Cancer (basal and squamous cell carcinomas), PTSD and HIV as stated in Press Releases[2] [3]:

> "Cannabis Science, Inc. is at the forefront of cannabinoid research and development for unmet medical needs. The Company works with leading experts in HIV drug development, medicinal characterization, and clinical research to develop, produce, and commercialize Phytocannabinoid-based pharmaceutical products. Cannabis Science is currently working with CBR International to develop a Pre-IND Application to the FDA that focuses on the use of CS-S/BCC-1 topical cannabis-based preparations for the treatment of basal and squamous cell carcinomas."

The Current CEO and president of Cannabis Science is Robert Melamede Ph.D. the former Chairman, and current professor, of the Biology Department at University of Colorado, Colorado Springs. Dr. Melamede is a renown cannabinoid researcher, and teaches a class on cannabinoids [4][5][6]. He recently spoke at the 7th Annual Patients Out of Time conference, giving a presentation on cannabis oil and skin cancer[7][8].

Products

Cannabis Science aims for two product groups, over the counter products for skin care and prescription products for serious illness.

Medical Products

The main product of Cannabis Science is medical Cannabis. More specifically, they hope to use whole cannabis extracts containing THC and Cannabidiol along with the entire spectrum of cannabinoids and accessory terpenes, etc. Although medical marijuana is available in many states, it remains illegal at the federal level. For it to be approved as medicine for all Americans (and by proxy most of the earth) it must be approved by the FDA, and Cannabis Science is moving forward for this[9].

Over The Counter products

On top of the medicinal products, they are also in the process of producing over the counter skin products including Lip Balm, Sun-Screen, lotions for Eczema and Psoriasis, and a moisturizing lotion. These will utilize hemp seed oil, and possible non-psychoactive cannabinoids such as CBD.

Patients

Cannabis Science currently has four skin cancer patients who have self medicated using topical Cannabis Oil, and have provided the public with pictures showing the healing progression. The results are staggering, patients have their cancers killed and healed without surgery or harmful side effects[10]. The results are especially dramatic for Patients two and three. Tumors, which begin under the skin, are pulled to the surface, killed and expelled by the topical application of the oil as shown in the images[11].

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GW Pharmaceuticals

GW Pharmaceuticals PLC

Traded as	LSE: GWP [1]
Industry	Pharmaceutical
Founded	1998
Founder(s)	Dr Geoffrey Guy and Dr Brian Whittle
Headquarters	United Kingdom Porton Down Science Park [2]
Key people	Justin Gover [3]
Products	Sativex®
Revenue	29.63$ million.[4]
Divisions	Biotechnology
Website	http://www.gwpharm.com/

GW Pharmaceuticals is a Biopharmaceutical company that patented the first prescription medicine derived from Cannabis sativa the product is trademarked by the name of Sativex® and it's currently being used for the treatment of Multiple Sclerosis and chronic pain.[5]

History

Background

In 1998, Dr Geoffrey Guy and Dr Brian Whittle founded GW Pharmaceuticals, that same year they obtained the only cultivation license in the United Kingdom from the Home Office and the MHRA, allowing GW Pharm to cultivate marijuana, from seeds and clones, and to conduct scientific research concerning the medicinal uses of the Cannabis plant. [6][7]

Hortapharm

On July 1998, GW pharm teamed up with Hortapharm B.V., a cannabis research and development business, based in the Netherlands,[8] founded by two expert horticulturists from California,[9] Robert Connell Clarke [10] and David Paul Watson also known as Sam the *Skunkman* [11] who where growing medicinal strains for the Dutch government.[12] [13] [14] [15]

Sativex®

Nabiximols (trade name Sativex) is a patented cannabinoid oromucosal mouth spray developed by GW Pharmaceuticals for multiple sclerosis (MS) patients, who can use it to alleviate neuropathic pain, spasticity, overactive bladder, and other symptoms. Nabiximols is also being developed in Phase III trials as a potential treatment to alleviate pain due to cancer. It has also been researched in various models of peripheral and central neuropathic pain, it is made with two unkwown cannabis strains and it's extracted with ethanol and Co2.[16][17]

Bayer

In 2011, GW pharm concluded a partnership with Bayer for the distribution of Sativex® in North America[18] and have an estimated production of 100 tons of medicinal cannabis each year since 2012.[19]

Patents

- Liquid formulations for mucosal administration of cannabinoids. [20]
- Use of the phytocannabinoid Cannabidiol (CBD) in combination with a standard anti-epileptic drug (SAED) in the treatment of Epilepsy.[21]
- Compositions comprising cannabinoid combinations and uses thereof [22]
- Compositions comprising combination of phyto-cannabinoids and uses thereof.[23]
- Use of the phytocannabinoid cannabidivarin (CBDV) in the treatment of epilepsy.[24]
- Phytocannabinoids in the treatment of cancer.[25]
- Anti-tumoural effects of cannabinoid combinations.[26]
- Cannabinoids in combination with non-Cannabinoid chemotherapeutic agents (E.G serm or alkylating agents).[27]
- Use of cannabinoids in combination with an anti-psychotic medicament.[28]
- Use of one or a combination of phyto-cannabinoids in the treatment of epilepsy [29]
- Pharmaceutical compositions containing a phyto-cannabinoid in combination with an anti- psychotic medicine [30]
- Anti-tumoural effects of cannabinoid combinations [31]
- Anti-tumoural effects of cannabinoid combinations [31]
- Cannabis based pharmaceutical formulation [32]
- Methods to purify cannabinoids from plant material.[33]
- New use for cannabinoid [34]
- New use for cannabinoids [35]
- Cannabis sativa piants rich in cannabi chromene and its acid, extracts thereof and methods of obtaining extracts therefrom [36]
- Uses of cannabidiol in the inhibition of brain tumor cell migration [37]
- Cannabidiol for use in the treatment of transmissible neurodegenerative conditions [38]
- New pharmaceutical formulation comprising cannabidiol and tetrahydrocannabidivarin [39]
- Use of tetrahydrocannabinol and/or cannabidiol for the treatment of inflammatory bowel disease.[40]
- Therapeutic uses of cannabigerol [41]
- A novel reference plant, a method for its production, extracts obtained therefrom and their use [42]
- New use for cannabinoid [43]
- Cannabinoids for use in the treatment of neuropathic pain [44]
- Use of pharmaceutical compositions comprising cannabigerol for the treatment of depression [45]
- New use for cannabinoid [46]
- Pharmaceutical composition containing cannabis and devices for delivering the same. [47]
- Process and apparatus for extraction of active substances and enriched extracts from natural products [48]
- Use of cannabinoids in the manufacture of medicaments [49]
- New use for cannabinoids [50]
- Cannabinoid-containing plant extracts as neuroprotective agents [51]
- Pharmaceutical compositions for the treatment of disease and/or symptoms in arthritis [52]
- A combination of cannabinoids for the treatment of peripheral neurophatic pain [53]
- A secure dispensing apparatus [54]
- Pharmaceutical compositions for the treatment of chronic obstructive pulmonary disease [55]

- A system for influencing and monitoring the movement of products [56]
- New use for cannabinoid [57]
- Inhibition of tumour cell migration [58]
- Pharmaceutical compositions [59]
- Cannabinoid liquid formulations for mucosal amdinistration [60]
- Extraction of pharmaceutically active cannabinoids from plant materials [61]
- Dispenser with reservoir containing a drug of abuse [62]
- Pharmaceutical compositions comprising cabbinochreme type compounds [63]
- New use for pharmaceutical composition [64]
- Methods of purifying cannabinoids from plant material [65]
- Method of preparing cannabidiol from plant material [66]
- Extraction of pharmaceutically active cannabinoids from plant materials [67]
- Cannabinoid liquid formulations for mucosal amdinistration [68]
- Pharmaceutical compositions [69]
- Mucoadhesive pharmaceutical formulations [70]
- Compositions comprising cannabinoids for treatment of nausea, vomiting, emesis, motion sickness or like conditions [71]
- Pharmaceutical compositions comprising cannabis [72]
- Inhalation of vapour of therapeutical substances, like e.g. cannabis extract [73]
- A device, method and resistive element for vaporising a medicament [74]
- Processes and apparatus for extraction of active substances and enriched extracts from natural products [75]
- Mucoadhesive pharmaceutical formulations [76]
- Secure dispensing apparatus [77]
- Pharmaceutical compositions comprising Cannabis [78]

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[11] http://www.bop.gov/iloc2/InmateFinderServlet?Transaction=NameSearch&needingMoreList=false&FirstName=david&Middle=& LastName=watson&Race=U&Sex=U&Age=&x=0&y=0 (DAVID A WATSON 49366-018 55-White-M UNKNOWN NOT IN BOP CUSTODY) david watson aka SKUNKMAN ?

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[15] http://www.fastcompany.com/magazine/79/cannabiswatson.html?page=0%2C0 Dr. Dope's Connection

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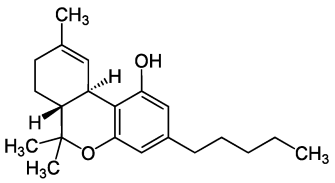
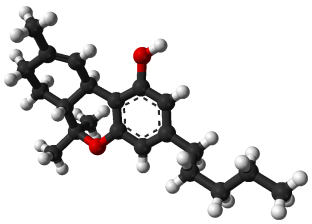
Tetrahydrocannabinol

Tetrahydrocannabinol (THC)





Systematic (IUPAC) name	
(−)-(6a*R*,10a*R*)-6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6*H*-benzo[*c*]chromen-1-ol	
Clinical data	
Pregnancy cat.	C
Legal status	Schedule I and III (US)
Dependence liability	8-10%[1]
Routes	Orally, Smoked (or vaporized)
Pharmacokinetic data	
Bioavailability	10-35% (inhalation), 6-20% (oral)[2]
Protein binding	95-99%[2]
Metabolism	mostly hepatic by CYP2C[2]
Half-life	1.6-59 h,[2] 25-36 h (orally administered Dronabinol)
Excretion	65-80% (feces), 20-35% (urine) as acid metabolites[2]
Identifiers	
CAS number	1972-08-3 [3] ✓
ATC code	A04AD10 [4]
PubChem	CID 16078 [5]
IUPHAR ligand	2424 [6]
DrugBank	DB00470 [7]
ChemSpider	15266 [8] ✓
UNII	7J8897W37S [9] ✓

ChEMBL	CHEMBL465 [10] ✓
Synonyms	Dronabinol
Chemical data	
Formula	$C_{21}H_{30}O_2$
Mol. mass	314.45
Physical data	
Boiling point	157 °C (315 °F) [11]
Solubility in water	0.0028[12] (23 °C) mg/mL (20 °C)
Spec. rot	-152° (ethanol)
✓ **(what is this?) (verify)** [13]	

Tetrahydrocannabinol (/ˌtɛtrəˌhaɪdrəkəˈnæbɪnɒl/ *tet-rə-**HY**-drə-kə-**NAB**-i-nol*; **THC**), also known as **delta-9-tetrahydrocannabinol** (**Δ^9-THC**), is the principal psychoactive constituent of the cannabis plant. First isolated in 1964,[14][15][16] in its pure form, it is a glassy solid when cold, and becomes viscous and sticky if warmed. Synthetically prepared THC, officially referred to by its INN, **dronabinol**, is available by prescription in the U.S. and Canada under the brand name **Marinol**. An aromatic terpenoid, THC has a very low solubility in water, but good solubility in most organic solvents, specifically lipids and alcohols.

Like most pharmacologically-active secondary metabolites of plants, THC in cannabis is assumed to be involved in self-defense, perhaps against herbivores[17] but as of now it is still unknown. THC also possesses high UV-B (280-315 nm) absorption properties, which, it has been speculated, could protect the plant from harmful UV radiation exposure.[18][19][20]

Pharmacology

The pharmacological actions of THC result from its partial agonist activity at the cannabinoid receptor CB_1, located mainly in the central nervous system, and the CB_2 receptor, mainly expressed in cells of the immune system.[21] The psychoactive effects of THC are primarily mediated by its activation of CB_1G-protein coupled receptors, which result in a decrease in the concentration of the second messenger molecule cAMP through inhibition of adenylate cyclase.[22]

The presence of these specialized cannabinoid receptors in the brain led researchers to the discovery of endocannabinoids, such as anandamide and 2-arachidonoyl glyceride (2-AG). THC targets receptors in a manner far less selective than endocannabinoid molecules released during retrograde signaling, as the drug has a relatively low cannabinoid receptor efficacy and affinity. In populations of low cannabinoid receptor density, THC may act to antagonize endogenous agonists that possess greater receptor efficacy.[23] THC is a lipophilic molecule and may bind non-specifically to a variety of receptors in the brain and body, such as adipose tissue. For a review of the mechanisms behind endocannabinoid synaptic transmission, see the endocannabinoid system.

Several studies have suggested that THC also has an anticholinesterase action[24][25] which may implicate it as a potential treatment for Alzheimer's and Myasthenia Gravis.

Effects

THC has mild to moderate analgesic effects, and cannabis can be used to treat pain by altering transmitter release on dorsal root ganglion of the spinal cord and in the periaqueductal gray.[22] Other effects include relaxation, alteration of visual, auditory, and olfactory senses, fatigue, and appetite stimulation (colloquially known as "the munchies"). It also has antiemetic properties, and also may reduce aggression in certain subjects.[26]

Due to its partial agonistic activity, THC appears to result in greater downregulation of cannabinoid receptors than endocannabinoids, further limiting its efficacy over other cannabinoids. While tolerance may limit the maximal effects of certain drugs, evidence suggests that tolerance develops irregularly for different effects with greater resistance for primary over side-effects, and may actually serve to enhance the drug's therapeutic window.[23] However, this form of tolerance appears to be irregular throughout mouse brain areas and warrants future research.

THC reduces male fertility in vivo, by inhibiting ATP production in sperm [27].

THC, as well as other cannabinoids that contain a phenol group possess mild antioxidant activity sufficient to protect neurons against oxidative stress, such as that produced by glutamate-induced excitotoxicity.[21]

Appetite and taste

It has long been known that in humans, cannabis increases appetite and consumption of food. The mechanism for appetite stimulation in subjects is believed to result from activity in the gastro-hypothalamic axis. CB1 activity in the hunger centers in the hypothalamus increases the palatability of food when levels of a hunger hormone ghrelin increase prior to consuming a meal. After chyme is passed into the duodenum, signaling hormones such as cholecystokinin and leptin are released, causing reduction in gastric emptying and transmission of satiety signals to the hypothalamus. Cannabinoid activity is reduced through the satiety signals induced by leptin release.

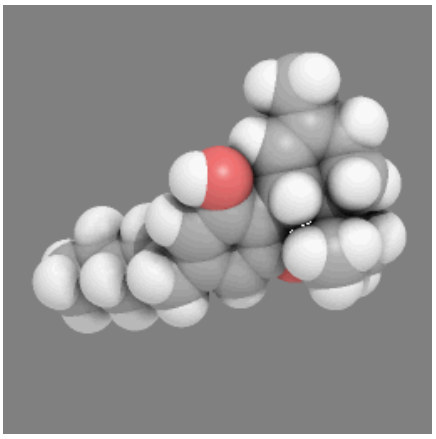
Based on the connection between palatable food and stimulation of dopamine (DA) transmission in the shell of the nucleus accumbens (NAc), it has been suggested that cannabis does not only stimulate taste, but possibly the hedonic value of food. A taste-reactivity paradigm in mice was used to investigate the influence of THC on DA release in the NAc upon application of sucrose or quinine solutions. THC application was found to enhance DA release in the NAc from sucrose, but not quinine, in a dose-dependent manner. This effect was enhanced with sweeter solution, which correlated with an increase the researchers' hedonic-behavior assessment as well. The mechanism behind this effect was elucidated by application of rimonabant, a CB_1 receptor inverse agonist, known to reduce intake of food or sweet solutions. However, the same DA enhancement effect was not found upon repeated application of sucrose, suggesting that the DA response undergoes habituation.[28] The inconsistency between DA habituation and enduring appetite observed after THC application suggests that cannabis-induced appetite stimulation is not only mediated by enhanced pleasure from platable food, but through THC stimulation of another appetitive response as well.

Antagonism

The effects of the drug can be suppressed by the CB_1 receptor antagonist rimonabant (SR141716A) as well as opioid receptor antagonists (opioid blockers) naloxone and naloxonazine.[29] The α_7 nicotinic receptor antagonist methyllycaconitine can block self-administration of THC in rats comparable to the effects of varenicline on nicotine administration.[30]

Toxicity

There has never been a documented human fatality from overdosing on tetrahydrocannabinol or cannabis in its natural form,[31] though the synthetic THC pill "Marinol" was cited by the FDA as being responsible for 4 deaths between January 1, 1997 and June 30, 2005.[32] Information about THC's toxicity is primarily based on results from animal studies. The toxicity depends on the route of administration and the laboratory animal. Absorption is limited by serum lipids, which can become saturated with THC, mitigating toxicity.[33] According to the Merck Index, 12th edition, THC has an LD_{50} (dose killing half of the research subjects) value of 1270 mg/kg (male rats) and 730 mg/kg (female rats) administered orally dissolved in sesame oil.[34] The LD_{50} value for rats by inhalation of THC is 42 mg/kg of body weight.[34]



3D rendering of the THC molecule

A Hybrid Cannabis Strain (White Widow) flower coated with trichomes, which contain more THC than any other part of the plant

Closeup of THC-filled trichomes on a *Cannabis Sativa* leaf

Animal	Administration	LD_{50} [mg/kg]
rat	oral	666 [33]
rat (male)	oral	1270 [34]
rat (female)	oral	730 [34]
rat	inhalation	42 [34]
rat	intraperitoneal	373 [33]
rat	intravenous	29 [33]
mouse	intravenous	42 [33]
mouse	oral	482 [33]
mouse	intraperitoneal	168 [33]
monkey (LDLo)	intravenous	128 [33]
dog	oral	525 [33]

Research

The discovery of THC was first described in "Isolation, structure and partial synthesis of an active constituent of hashish", published in the Journal of the American Chemical Society in 1964.[14] Research was also published in the academic journal *Science*, with "Marijuana chemistry" by Raphael Mechoulam in June 1970,[35] followed by "Chemical basis of hashish activity" in August 1970.[36] In the latter, the team of researchers from Hebrew University Pharmacy School and Tel Aviv University Medical School experimented on monkeys to isolate the active compounds in hashish. Their results provided evidence that, except for tetrahydrocannabinol, no other major active compounds were present in hashish.

Studies in humans

A number of studies show that THC provides medical benefits for cancer and AIDS patients by increasing appetite and decreasing nausea. It has also been shown to assist some glaucoma patients by reducing pressure within the eye, and is used in the form of cannabis by a number of multiple sclerosis patients, who use it to alleviate neuropathic pain and spasticity. The National Multiple Sclerosis Society is currently supporting further research into these uses.[37]

In August 2009 a phase IV clinical trial by the Hadassah Medical Center in Jerusalem, Israel started to investigate the effects of THC on post-traumatic stress disorders.[38] THC and other cannabinoid agonists have been shown to be beneficial both in open label studies, as well as in laboratory experiments with animals to ameliorate post-traumatic stress disorders.

Preliminary research on synthetic THC has been conducted on patients with Tourette syndrome, with results suggesting that it may help in reducing nervous tics and urges by a significant degree. Research on twelve patients showed that Marinol reduced tics with no significant adverse effects. A six-week controlled study on 24 patients showed that the patients taking dronabinol had a significant reduction in tic severity without serious adverse effects. More significant reduction in tic severity was reported with longer treatment. No detrimental effects on cognitive functioning and a trend towards improvement in cognitive functioning were reported during and after treatment.

Dronabinol's usefulness as a treatment for Tourette syndrome cannot be determined until/unless longer controlled studies on larger samples are undertaken.[39][40][41]

Research on THC has shown that Cannabinoid receptors are responsible for mediated inhibition of dopamine release in the retina.[42]

In a 1981 double-blind, placebo-controlled study, oral THC was given to Multiple Sclerosis patients. A decrease in spasticity was shown when compared with placebo.[43] In a 1983 single-blind, placebo-controlled study, decreased tremor occurred in 1/4 of Multiple Sclerosis patients.[44]

Several studies have been conducted with spinal injury patients and THC. Decreased tremor occurred in 2/5 patients in a 1986 double-blind, placebo-controlled crossover study.[45] THC was shown to decrease spasticity and pain in a 1990 double-blind, placebo-controlled study[46]

Studies in animals and in vitro

New scientific evidence is showing that THC can prevent Alzheimer's Disease in an animal model by preventing the inflammation caused by microglia cells which are activated by binding of amyloid protein.[47]

In *in-vitro* experiments, THC at extremely high concentrations, which could not be reached with commonly-consumed doses, caused inhibition of plaque formation (which are associated with Alzheimer's disease) better than currently-approved drugs.[48]

THC may also be an effective anti-cancer treatment, with studies showing tumor size reduction in mice conducted in 1975[49] and 2007,[50] as well as in a pilot study in humans with glioblastoma multiforme (a type of brain cancer).[51] THC has also been found to attenuate conditioned retching and sickness, experimentally verifying anecdotal reports that THC alleviates nausea and vomiting when undergoing chemotherapy.[52]

A two-year study in which rats and mice were force-fed tetrahydrocannabinol dissolved in corn oil showed reduced body mass, enhanced survival rates, and decreased tumor incidences in several sites, mainly organs under hormonal control. It also caused testicular atrophy and uterine and ovarian hypoplasia, as well as hyperactivity and convulsions immediately after administration, of which the onset and frequency were dose related.[53]

Research in rats indicates that THC prevents hydroperoxide-induced oxidative damage as well as or better than other antioxidants in a chemical (Fenton reaction) system and neuronal cultures.[54] In mice low doses of Δ^9-THC reduces the progression of atherosclerosis.[55]

Research has also shown that past claims of brain damage from cannabis use fail to hold up to the scientific method.[56] Instead, recent studies with synthetic cannabinoids show that activation of CB1 receptors can facilitate neurogenesis,[57] as well as neuroprotection,[58] and can even help prevent natural neural degradation from neurodegenerative diseases such as MS, Parkinson's, and Alzheimer's. This, along with research into the CB2 receptor (throughout the immune system), has given the case for medical marijuana more support.[59][60] THC is both a CB1 and CB2 agonist.[61]

Scientific studies indicating side-effects

Conceivable long-term ill effects of THC on humans are disputed, yet its status as an illegal drug in most countries can make research difficult, for instance in the United States where the National Institute on Drug Abuse is the only legal source of cannabis for researchers.[62]

Some studies claim a variety of negative effects associated with long-term use, including short-term memory loss.[63][64] Some studies have found little or no difference in MRI scans between user groups and non-using control groups. Using positron emission tomography (PET), one study reports altered memory-related brain function (23% better memory for the cannabis users in recalling the end of a list of things to remember, but 19% worse memory for cannabis users in recalling the middle of a list of things to remember) in chronic daily cannabis users.[65]

Some studies have suggested that cannabis users have a greater risk of developing psychosis than non-users. This risk is most pronounced in cases with an existing risk of psychotic disorder.[66] Other studies have made similar associations, especially in individuals predisposed to psychosis prior to cannabis use.[67] A 2005 paper from the

Dunedin study suggested an increased risk in the development of psychosis linked to polymorphisms in the COMT gene.[68] However, a more recent study cast doubt on the proposed connection between this gene and the effects of cannabis on the development of psychosis.[69]

A 2008 German review reported that cannabis was a causal factor in some cases of schizophrenia and stressed the need for better education among the public due to increasingly relaxed access to cannabis.[70] Though cannabis use has increased dramatically in several countries over the past few decades, the rates of psychosis and schizophrenia have not generally increased, casting some doubt over whether the drug can cause cases that would not otherwise have occurred.[71]

Conversely, research from 2007 reported a correlation between cannabis use and *increased* cognitive function in schizophrenic patients.[72]

A 2008 National Institutes of Health study of 18 chronic heavy marijuana users with cardiac and cerebral abnormalities (averaging 28g to 272g (1 to 8 oz) weekly) and 24 controls found elevated levels of apolipoprotein C-III (apoC-III) in the chronic smokers.[73] An increase in apoC-III levels induces the development of hypertriglyceridemia.

A 2008 study by the University of Melbourne of 15 heavy marijuana users (consuming at least 5 marijuana cigarettes daily for on average 20 years) and 16 controls found an average size difference for the smokers in the hippocampus (12 percent smaller) and the amygdala (7 percent smaller).[74] It has been suggested that such effects can be reversed with long term abstinence.[75] However, the study indicates that they are unsure that the problems were caused by marijuana alone.

A 2008 study at Karolinska Institute suggested that young rats treated with THC received an increased motivation for drug use, heroin in the study, under conditions of stress.[76][77]

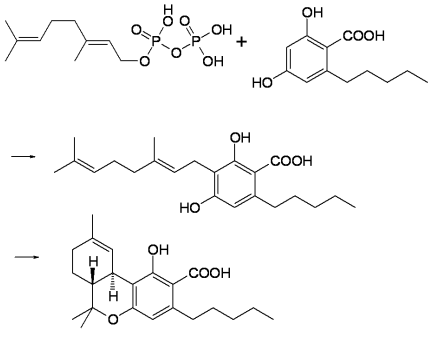
Opinions and statistical observations indicating side-effects

A literature review on the subject concluded that "Cannabis use appears to be neither a sufficient nor a necessary cause for psychosis. It is a component cause, part of a complex constellation of factors leading to psychosis."[78] Likewise, a French review from 2009 came to a conclusion that cannabis use, particularly that before age 15, was a factor in the development of schizophrenic disorders.[79]

A 2009 study found that there was a high prevalence of cannabis in the toxicologic analysis of homicide (22%) and suicide victims (11%) in Australia.[80] In a similar study from Sweden it was also found that suicide victims had a significantly higher use of cannabis, but the authors found that "this was explained by markers of psychological and behavioural problems."[81]

Biosynthesis

In the cannabis plant, THC occurs mainly as tetrahydrocannabinolic acid (THCA, 2-COOH-THC). Geranyl pyrophosphate and olivetolic acid react, catalysed by an enzyme to produce cannabigerolic acid,[82] which is cyclized by the enzyme THC acid synthase to give THCA. Over time, or when heated, THCA is decarboxylated producing THC. The pathway for THCA biosynthesis is similar to that which produces the bitter acid humulone in hops.[83] [84]



Biosynthesis of THC

Natural occurrence

Cannabis indica may have a CBD:THC ratio 4–5 times that of *Cannabis sativa*. Cannabis strains with relatively high CBD:THC ratios are less likely to induce anxiety than vice versa. This may be due to CBD's antagonistic effects at the cannabinoid receptors, compared to THC's partial agonist effect. CBD is also a 5-HT_{1A} receptor agonist, which may also contribute to an anxiolytic effect.[85] This likely means the high concentrations of CBD found in *Cannabis indica* mitigate the anxiogenic effect of THC significantly.[85] The effects of *sativa* are well known for its cerebral high, hence used daytime as medical cannabis, while *indica* are well known for its sedative effects and preferred night time as medical cannabis.[85]

Metabolism

THC is metabolized mainly to 11-OH-THC by the body. This metabolite is still psychoactive and is further oxidized to 11-nor-9-carboxy-THC (THC-COOH). In humans and animals, more than 100 metabolites could be identified, but 11-OH-THC and THC-COOH are the dominating metabolites. Metabolism occurs mainly in the liver by cytochrome P450 enzymes CYP2C9, CYP2C19, and CYP3A4. More than 55% of THC is excreted in the feces and ~20% in the urine. The main metabolite in urine is the ester of glucuronic acid and THC-COOH and free THC-COOH. In the feces, mainly 11-OH-THC was detected.[86]

11-OH-THC may also play a role in the psychoactive effects of cannabis.

Detection in body fluids

THC, 11-OH-THC and THC-COOH can be detected and quantitated in blood, urine, hair, oral fluid or sweat using a combination of immunoassay and chromatographic techniques as part of a drug use testing program or in a forensic investigation of a traffic or other criminal offense or suspicious death. [87][88][89]

Marinol

Dronabinol is the INN for a pure isomer of THC, (−)-*trans*-Δ^9-tetrahydrocannabinol, which is the main isomer found in cannabis.[90] It is sold as **Marinol** (a registered trademark of Solvay Pharmaceuticals). Dronabinol is also marketed, sold, and distributed by PAR Pharmaceutical Companies under the terms of a license and distribution agreement with SVC pharma LP, an affiliate of Rhodes Technologies. Synthesized THC may be generally referred to as *dronabinol*. It is available as a prescription drug (under Marinol[91]) in several countries including the United States and Germany. In the United States, Marinol is a Schedule III drug, available by prescription, considered to be non-narcotic and to have a low risk of physical or mental dependence. Efforts to get cannabis rescheduled as analogous to Marinol have not succeeded thus far, though a 2002 petition has been accepted by the DEA. As a result of the rescheduling of Marinol from Schedule II to Schedule III, refills are now permitted for this substance. Marinol has been approved by the U.S. Food and Drug Administration (FDA) in the treatment of anorexia in AIDS patients, as well as for refractory nausea and vomiting of patients undergoing chemotherapy, which has raised much controversy as to why natural THC is still a schedule I drug.[92]

An analog of dronabinol, nabilone, is available commercially in Canada under the trade name Cesamet, manufactured by Valeant Pharmaceuticals. Cesamet has also received FDA approval and began marketing in the U.S. in 2006; it is a Schedule II drug.

In April 2005, Canadian authorities approved the marketing of Sativex, a mouth spray for multiple sclerosis patients, who can use it to alleviate neuropathic pain and spasticity. Sativex contains tetrahydrocannabinol together with cannabidiol and is a preparation of whole cannabis rather than individual cannabinoids. It is marketed in Canada by GW Pharmaceuticals, being the first cannabis-based prescription drug in the world (in modern times). In addition, Sativex received European regulatory approval in 2010.[93]

Comparisons to medical marijuana

Female cannabis plants contain more than 60 cannabinoids, including cannabidiol (CBD), thought to be the major anticonvulsant that helps multiple sclerosis patients;[94] and cannabichromene (CBC), an anti-inflammatory which may contribute to the pain-killing effect of cannabis.[95]

It takes over one hour for Marinol to reach full systemic effect,[96] compared to seconds or minutes for smoked or vaporized cannabis.[97] Some patients accustomed to inhaling just enough cannabis smoke to manage symptoms have complained of too-intense intoxication from Marinol's predetermined dosages. Many patients have said that Marinol produces a more acute psychedelic effect than cannabis, and it has been speculated that this disparity can be explained by the moderating effect of the many non-THC cannabinoids present in cannabis. For that reason, alternative THC-containing medications based on botanical extracts of the cannabis plant such as nabiximols are being developed. Mark Kleiman, director of the Drug Policy Analysis Program at UCLA's School of Public Affairs said of Marinol, "It wasn't any fun and made the user feel bad, so it could be approved without any fear that it would penetrate the recreational market, and then used as a club with which to beat back the advocates of whole cannabis as a medicine."[98] United States federal law currently registers dronabinol as a Schedule III controlled substance, but all other cannabinoids remain Schedule I, excepting synthetics like nabilone.

Regulatory history

Since at least 1986, the trend has been for THC in general, and especially the Marinol preparation, to be downgraded to less and less stringently-controlled schedules of controlled substances, in the U.S. and throughout the rest of the world.

On July 13, 1986, the Drug Enforcement Administration (DEA) issued a Final Rule and Statement of Policy authorizing the "Rescheduling of Synthetic Dronabinol in Sesame Oil and Encapsulated in Soft Gelatin Capsules From Schedule I to Schedule II" (DEA 51 FR 17476-78). This permitted medical use of Marinol, albeit with the severe restrictions associated with Schedule II status. For instance, refills of Marinol prescriptions were not permitted. At its 1045th meeting, on April 29, 1991, the Commission on Narcotic Drugs, in accordance with article 2, paragraphs 5 and 6, of the Convention on Psychotropic Substances, decided that Δ^9-tetrahydrocannabinol (also referred to as Δ^9-THC) and its stereochemical variants should be transferred from Schedule I to Schedule II of that Convention. This released Marinol from the restrictions imposed by Article 7 of the Convention (See also United Nations Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances).

An article published in the April–June 1998 issue of the Journal of Psychoactive Drugs found that "Healthcare professionals have detected no indication of scrip-chasing or doctor-shopping among the patients for whom they have prescribed dronabinol". The authors state that Marinol has a low potential for abuse.[99]

In 1999, Marinol was rescheduled from Schedule II to III of the Controlled Substances Act, reflecting a finding that THC had a potential for abuse less than that of cocaine and heroin. This rescheduling comprised part of the argument for a 2002 petition for removal of cannabis from Schedule I of the Controlled Substances Act, in which petitioner Jon Gettman noted, "Cannabis is a natural source of dronabinol (THC), the ingredient of Marinol, a Schedule III drug. There are no grounds to schedule cannabis in a more restrictive schedule than Marinol".[100]

At its 33rd meeting, in 2003, the World Health Organization Expert Committee on Drug Dependence recommended transferring THC to Schedule IV of the Convention, citing its medical uses and low abuse potential.[101]

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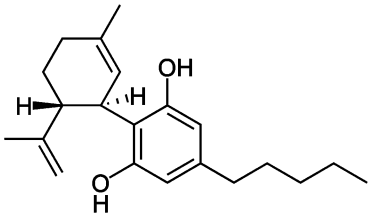
- Petition to Reschedule Cannabis (Marijuana) per 21 CFR §1308.44(b) (http://www.drugscience.org/pt/b.htm), Filed October 9, 2002 with the DEA by the Coalition for Rescheduling Cannabis.

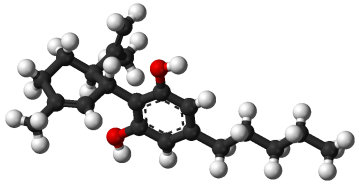
External links

- U.S. National Library of Medicine: Drug Information Portal - Tetrahydrocannabinol (http://druginfo.nlm.nih.gov/drugportal/dpdirect.jsp?name=Tetrahydrocannabinol)

Cannabidiol

Cannabidiol





Systematic (IUPAC) name	
2-[(1*R*,6*R*)-6-isopropenyl-3-methylcyclohex-2-en-1-yl]-5-pentylbenzene-1,3-diol	
Clinical data	
AHFS/Drugs.com	International Drug Names [1]
Pregnancy cat.	?
Legal status	Schedule II (Can)
Identifiers	
CAS number	13956-29-1 [2] ✓
ATC code	None
PubChem	CID 644019 [3]
DrugBank	none [4]
ChemSpider	24593618 [5] ✓
UNII	19GBJ60SN5 [6] ✓
Chemical data	
Formula	$C_{21}H_{30}O_2$
Mol. mass	314.46
Physical data	
Melt. point	66 °C (151 °F)
Boiling point	180 °C (356 °F) (Range: 160°C-180°C) [7]

✗ **(what is this?) (verify)** [8]

Cannabidiol (**CBD**) is a cannabinoid found in cannabis. It is a major constituent of the plant, representing up to 40% in its extracts.[9]

It has displayed sedative effects in animal tests.[10] Some research, however, indicates that CBD can increase alertness.[11] It may decrease the rate of THC clearance from the body, perhaps by interfering with the metabolism of THC in the liver.

Medically, it has been shown to relieve convulsion, inflammation, anxiety, and nausea, as well as inhibit cancer cell growth.[12] Recent studies have shown cannabidiol to be as effective as atypical antipsychotics in treating schizophrenia.[13] Studies have also shown that it may relieve symptoms of dystonia.[14][15]

In November 2007, it was reported that CBD reduces growth of aggressive human breast cancer cells *in vitro* and reduces their invasiveness.

A 2008 study published in the British Journal of Psychiatry showed significant differences in the Oxford-Liverpool Inventory of Feelings and Experiences scores between three groups: the first consisted of non-cannabis users, the second consisted of users with THC detected, and the third consisted of users with both THC and CBD detected. The THC only group scored significantly higher for unusual experiences than the THC and CBD group, whereas the THC and CBD group had significantly lower introvertive anhedonia scores than the THC only group and non-cannabis user group. This research indicates that CBD acts as an anti-psychotic and may counteract the potential psychotomimetic effects of THC on individuals with latent schizophrenia.[16]

Medicinal use

Cannabidiol is shown to decrease activity of the limbic system[17] and to decrease social isolation induced by THC.[18] It's also shown that Cannabidiol reduces anxiety in social anxiety disorder. [19] [20] In April 2005, Canadian authorities approved the marketing of Sativex, a mouth spray for multiple sclerosis to alleviate pain. Sativex contains tetrahydrocannabinol together with cannabidiol. It is marketed in Canada by GW Pharmaceuticals.

In 1985 a single case study suggested that CBD may be effective in the management of levodopa-induced dyskinesia in a Parkinson's Disease patient.[21]

Studies have shown that CBD may reduce schizophrenic symptoms in patients, likely due to their apparent ability to stabilize disrupted or disabled NMDA receptor pathways in the brain, which are shared and sometimes contested by norepinephrine and GABA.[13][22] Leweke *et al.* performed a double blind, 4 week, explorative controlled clinical trial to compare the effects of purified cannabidiol and the atypical antipsychotic amisulpride on improving the symptoms of schizophrenia in 42 patients with acute paranoid schizophrenia. Both treatments were associated with a significant decrease of psychotic symptoms after 2 and 4 weeks as assessed by Brief Psychiatric Rating Scale and Positive and Negative Syndrome Scale. While there was no statistical difference between the two treatment groups, cannabidiol induced significantly fewer side effects (extrapyramidal symptoms, increase in prolactin, weight gain) when compared to amisulpride.[23]

Cannabidiol has also been shown as being effective treating an often drug-induced set of neurological movement disorders known as dystonia.[15] In one study, five out of five participants showed noted improvement in their dystonic symptoms by 20-50%.[14] CBD also appears to protect against 'binge' alcohol induced neurodegeneration.[24][25]

Cannabidiol may block THC's interference with memory.[26]

Pharmacology

Cannabidiol has no affinity for CB_1 and CB_2 receptors but acts as an indirect antagonist of cannabinoid agonists.[12] Recently it was found to be an antagonist at the putative new cannabinoid receptor, GPR55, a GPCR expressed in the caudate nucleus and putamen.[27] Cannabidiol has also been shown to act as a $5\text{-}HT_{1A}$ receptor agonist,[28] an action which is involved in its antidepressant,[29][30] anxiolytic,[30][31] and neuroprotective[32][33] effects. Cannabidiol is also an allosteric modulator at the Mu and Delta opioid receptor sites.[34]

Cannabidiol has also been shown to inhibit cancer cell growth with low potency in non-cancer cells. Although the inhibitory mechanism is not yet fully understood, Ligresti et al. suggest that "cannabidiol exerts its effects on these cells through a combination of mechanisms that include either direct or indirect activation of CB_2 and TRPV1 receptors, and induction of oxidative stress, all contributing to induce apoptosis."[35] In November 2007, researchers at the California Pacific Medical Center reported that CBD shows promise for controlling the spread of metastatic breast cancer. *In vitro* CBD downregulates the activity of the gene ID1 which is responsible for tumor metastasis.[36]

Chemistry

Cannabidiol is insoluble in water but soluble in organic solvents, such as pentane. At room temperature it is a colorless crystalline solid.[37] In strongly basic medium and the presence of air it is oxidized to a quinone.[38] Under acidic conditions it cyclizes to THC.[39] The synthesis of cannabidiol has been accomplished by several research groups.[40][41][42]

Biosynthesis

Cannabis produces CBD-carboxylic acid through the same metabolic pathway as THC, until the last step, where CBDA synthase performs catalysis instead of THCA synthase.[43]

Natural occurrence

Cannabis indica may have a CBD:THC ratio 4–5 times that of *Cannabis sativa*. Cannabis strains with relatively high CBD:THC ratios are less likely to induce anxiety than vice versa. This may be due to CBD's antagonistic effects at the cannabinoid receptors, compared to THC's partial agonist effect. CBD is also a $5\text{-}HT_{1A}$ receptor agonist, which may also contribute to an anxiolytic effect.[44] This likely means the high concentrations of CBD found in *Cannabis indica* mitigate the anxiogenic effect of THC significantly.[44] The effects of *sativa* are well known for its cerebral high, hence used daytime as medical cannabis, while *indica* are well known for its sedative effects and preferred night time as medical cannabis.[44]

Legal Status

Cannabidiol is a Schedule 2 Drug in Canada.[45]

The bud of a *Cannabis sativa* flower coated with trichomes, which contain more CBD than any other part of the plant.

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